Epidemiology of Cardiovascular Diseases Methodology

hypertension and arteriosclerosis

Guest Editors Herbert Pollack M D and Dean E Krueger

EPIDEMIOLOGY OF CARDIOVASCULAR DISEASES

CONTENTS

PREFACE

THE *Conference on Methodology in* Epidemiological Studies of Cardiovascular Diseases was devoted to problems of measurement in selected aspects of these studies Held at the Princeton Inn Princeton N J April 24 26 1959 it was cosponsored by the American Heart Association and the National Heart Institute United States Public Health Service

Subjects considered include criteria for the diagnosis and clinical evaluation of arteriosclerotic heart disease and hypertension dietary physical activity and biochemical measurements assessment of cultural societal familial psychological and genetic influences and general problems of design of studies and analysis of data

This is the report on the third conference cosponsored by the two organizations and directed to research on cardiovascular diseases The First National Conference on Cardiovascular Diseases held January 18 20 1950 in Washington was concerned with the entire range of technical knowledge and research community services and facilities professional education and with all cardiovascular diseases[1] The Conference on Epidemiology of Atherosclerosis and *Hypertension at Arden House Harriman* N Y January 29 February 2 1956 reviewed current etiological concepts in those diseases and tools available for studies of population groups to test those concepts and provide new leads for further investigation By 1957 several groups had either begun or were planning long term studies of cardiovascular diseases in population groups (Representatives of these groups met at the Hotel Beaconsfield Brookline Mass June 17 18 1957 at the invitation of the Framingham Heart Disease Epidemiology Study National Heart Institute to exchange information and consider problems of diagnostic *criteria and clinical and laboratory procedures*)[3]

With this background of interest and experience in epidemiological research in cardiovascular diseases the cosponsoring organizations felt that the time had *come to devote specific attention to* problems of measurement faced by individual investigations and to the potential value of being able to combine or at least compare results of several investigators using standard measurements The conference worked toward this goal not with the idea of selecting the best method for measuring any factor which might be important in epidemiological studies of cardiovascular diseases but by considering all available methods giving their judgment about minimum base line measurements which should be included in every epidemiological study of cardiovascular diseases and about optimum measurements which should be made in some studies when the circumstances enable use of these more precise methods

Prior to the conference nine working groups met to consider problems in the subject areas noted above and prepared preliminary reports for presentation to the conference Members of the Com*mittee on Design and Analysis of Studies* participated in meetings of each of the other groups This was a highly productive preconference activity I wish to express my appreciation to each of the 60 people who contributed to the preconference work as members of committees and especially to the chairmen of these groups to Dr Herbert Pollack chairman of the conference and to Mr Dean E Krueger executive secretary All of these as well as other persons who attended the conference are listed following this preface

The report of each of the nine groups which met prior to the conference was presented and discussed at length in

general e ion Each group au_mented by other conference participants who were particularly interested in the sul ject area al o met eparately to con ider the preliminary report and the di cus ion in general sea ion Revi ed reports were presented at the clo ing general es ion

This publication al.o reflects work by committee chairmen and in some in tance committee members after the conference a well as the continuing attention of the editors and technical a i tance from the Heart Informa tion Center National Heart In titute Mr Mary Howes National Heart In titute provided ecretarial ervice prior to and during the conference and typed the manu cript of this report

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REFERENCES

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2 D h T R (Ed) R p f th C l e Lo g d l C d e f S d R l B 6 l B a kl M ( ) l 18) 1 8 (d pl d)

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CHAIRMAN S ADDRESS

Herbert Pollack M D F A P H A

I WANT to welcome you to this Conference on Methodology in Epidemiological Studies of Cardiovascular Disease. One might ask: How did this Conference get started and who parked it into being? The point of origin would appear to be a letter from Dr. A. C. Corcoran to Dr. James Watt written by Dr. Corcoran shortly after returning from a visit to the School of Public Health at the University of Michigan in July 1958. Dr. Corcoran wrote that while there he had discussed the urgent need for standardization of procedures in cardiovascular surveys. This letter set in motion the machinery which resulted in this meeting.

Although the purposes of this conference have been explained to you I should like to restate them briefly.

One: to set up minimum acceptable baseline measures in specific areas thus providing comparability in epidemiological surveys. Two: to suggest optimum procedures. Three: to define gaps in methodology and to suggest studies to fill these gaps. During the deliberations of this conference we should continuously bear in mind these major objectives which will govern the final report.

The chairman wishes to express at this point his deep appreciation for the hard work of the many persons responsible for the administrative and operational chores involved in a meeting of this type. This conference is sponsored by the American Heart Association and the National Institutes of Health through the National Heart Institute. Mr. Dean Krueger executive secretary is basically responsible for most of what has taken place. Dr. William Zukel, Dr. John Ferree and many others have devoted a tremendous amount of time to the organization of this meeting—the happy culmination of which we see here.

In Biblical times the concept of the relationship of the environment to the individual and the individual to the environment was stated somewhat differently than it is today. Formerly the phrase "The world the flesh and the devil" was used. Today we discuss the environment the host and the cause of the disease. The health of the community as well as the diseases of the community are expressions of the relationship between the three factors enumerated. Even in Biblical times there was a concept of the epidemiological or the ecological approach to disease.

To fully understand the variations of the incidence of many diseases one must draw upon world experience rather than the small segment represented by a given community. Diseases and disease states, how many variations depending on environmental conditions under which they are observed. The epidemiological approach—based upon the ecology of the individual—makes use of the many types of data, it uses the methods of all the scientific disciplines represented here today: clinical medicine, statistics, social science, pathology, biochemistry, experimental physiology, *and many others*.

Those attending this conference recognize that in the history of medicine no disease has ever been conquered by an attempt to treat every affected individual. It is only by studying the etiology through the epidemiological approach that man has been able to stamp

out ma s di ea e It i hoped that this approach can be applied to the problem of cardiovascular disease

One purpo ■ of this conference is to point out to tho ■ interested in this area of *investigation the que tions that* remain to be answered Certain criteria will be set up which can be made ap plicable to lar,e area as tandard for the collection of data If we are to compare data from one area of the country with that from another or data from one part of the world with that from another obvious lv the e mu t be collected with such compari ons in mind Standard u ed in all tudies when re porting deviations from the normal hould be mutually acceptable and under tandable o that end results can l e meaningful in all countries to u e different tandards in various parts of the world is like conversing in different languages without a tran lator

As chairman I am enthusia tic at the opportunity of working side by side with pecialists from the many disciplines repre ented here It is a challenge— and al o a real problem in coordination Put then the e sence of good epidemi ological re earch is the coordination of many speciali ts toward a common goal One mu ■ not minimize the value of per onal views the concept that permits any person to report but only certain ones to advi ■ is unacceptible for this meeting If it were acceptable it would result in too ,reat a reliance on so called tudy groups of all types

While this is a new panel it can al o be viewed as a hi torical exten ion of *the Brooklin Conference Let us not* therefore fall into the error of many new panel that act as if nothing had ever l een done before—perhap becau ■ the continued exi tence of the problem l efore the panel i taken by ome a an indication of the inadequacy of previou conferences

The effective results of a conference of thi type depend not only on the con tributions of each participant but on omething even more important namely the working relationship of each indi vidual to his fellow members and to the group The value of the final report *could be negated if the individual prob* lems of peciali ts became i olated from the group and each problem were di posed of in its own way—by expert to be sure—but by experts who e only in tere t i the pecial difficulties involved in their own particular area

Conferences of this type can be ex traordinarily u eful not only can they provide us with fre h points of view but they can al ■ provide u with an excel lent way of locating talent that would otherwi e be unavailable The number of out tanding individuals with experi ence in any one field is limited As a result the ame group is called upon time and time again to review the ■ and related ta ks The type of panel pre ent today is omewhat different from the u ual one Usually in panel delibera tions the que tion tands or fall on the kill with which it is pre ented Hence there is a premium for quickness of com prehension by the uccess ful committee man Here we hope that the more important *quality of reflectiveness* rather than fluency in peaking will pre dominate

There will be a further difference from previous panels Usually panel are expected to adjust differences that exist between participant therefore it is not urpri ing to find them ending up with a re olution which is a common denominator rather than a well rounded *creative point of view I hope we will* not return to the common denominator type of resolution If we do not thi conference will contribute an important concept to the technic of solving prol lem

The development of hort term expedi ence i not the purpo e of this confer ence nor are we attemptin, to fin l Utopia where all questions will l e

answered and all problem olved We are not looking for the registration of di enting points of view We do seek from you a significant contribution to the field which will give a sense of direction to the development of epi demiological method for study of the cardiovascular di ea es

In bringing together the variou dis ciplines for this conference we hope that each of you will have the opportunity to pre ent your mo t important con iderations and t under tand the point of view of other di ipline It will be necessary to place a premium on those phases of other di ciplines which can not be most ea ily duplicated by your own Personally I would recommend that you listen particularly to phases of ancillary di ciplines which are unrelated to your own—these are the ones that require integration into your own field of expertnes The peculation which we eek can exi t only when the facts are not known with the development of these fact the area of peculation are gradually narrowed and then di appear

FRAME OF REFERENCE OF CONFERENCE COMMITTEE REPORTS

THE committees took advantage of reports on prior conferences on cardiovascular disease research in the United States cited in the Preface as well as those by Expert Committees of the World Health Organization to which some of the committee reports refer The scientific knowledge of members of the committees, however provide the major basis for this report

The committee reports reflect the information most acceptable to participants in the conference and in general their consensus regarding the adequacy and limitations of presently available methods and their ideas about research needed to improve or develop new methods

Credit and responsibility for the content of these committee reports rests primarily with the chairmen and secondarily with committee members and other participants in the conference

A special note is in order about the report of the Committee on Cultural Societal Familial Psychological and Genetic Influences on Cardiovascular Diseases Diverse scientific disciplines —in many instances represented by one person—were included in this group The report is presented as the chairman's interpretation of information provided by members of his committee coupled with his own broad knowledge of the subject It did not seem feasible in the limited time available to attempt to arrive at a synthesis of ideas on methodology in an area of study in which there are so many unknowns

COMMITTEE ON DESIGN AND ANALYSIS OF STUDIES

Felix E Moore [A.P.H.A] Chairman

It is clear that the problem of design and analysis in epidemiological studies of long-term disease are so varied and complex that nothing short of a lengthy treatise could provide adequate coverage. Such a treatise has not yet been written and its formulation is clearly outside the capabilities of an ad hoc committee meeting for a limited period. The committee has concerned itself therefore with a small number of rather general problems which appear to be recurring ones in this type of investigation. These are dealt with under two main headings: I. General Problems of Definition and Design and II. Measurement Problems. The committee has also considered it necessary to confine its attention to those studies which are based on the clinical or pathological examination of individuals thus omitting from consideration the types of studies based primarily on information secured by lay interviewers from household informants (morbidity surveys) and the types of studies based primarily on information from death certificates (mortality studies).

I. General Problems of Definition and Design

A. Some General Characteristics of Epidemiological Studies

Many types of studies which have contributed to advances in our knowledge of cardiovascular diseases have been termed epidemiological. There appear to be common elements of design which characterize these studies and common problems in the interpretation of results which differentiate them from other approaches to the study of disease. The committee believes that it will be more profitable to outline these common elements and problems than to attempt to formulate a narrow definition.

Epidemiological studies have been referred to variously as descriptive studies, population surveys, studies of association rather than causation, and have been contrasted with clinical or laboratory studies or controlled experiments. Each of these terms has connotations which undoubtedly will vary from one investigator to another. By way of clarification of the concept the committee suggests that the following elements are characteristic of epidemiological studies.

1. In an epidemiological study the subjects studied include not only persons known to have the disease under consideration but also persons who are free (or apparently free)* of the disease as well. This makes possible the search for factors which differentiate the two groups or alternatively the search for factors differentiating the subgroup among those free of disease who subsequently develop recognizable disease from the subgroup of those who do not. A frequent implication of the term

* In order to free the text of this report from the recurring circumlocution apparently free of disease the terms free of disease or "not diseased" will be used as labels for those persons in whom signs of cardiovascular disease (arteriosclerotic or hypertensive as appropriate) cannot be observed by standard clinical or laboratory methods of assessment. It is recognized that this begs an important question which is discussed in section II-A of this report.

clinical tudy is that it is concerned only with the group which seeks medi cal attention for disea e yet in many clinical tudies a di ease group is compared with a control group The difference if any lies in the method by which the tudy groups are selected and the breadth of generalization which that election permit ince epidemiologi al studies frequently require exhau tive clinical method of evaluation (See ections IA2 and IID for further elabora tion of this point)

2 The ideal epidemiological tudy would be based on probability amples from a very large population in order to permit generalization from the tudy group to the larger population with pecifiable limits of precision It is rare however that the ideal approach is po sible the circumstances under which epidemiological tudies can be conducted often do not permit the draw ing of random amples from the very large population to which it would be desirable to generalize It is important to recognize therefore that generaliza bility is a relative matter rarely in *practice* will *generalizations* apply to broader populations without ome re strictions Knowled e of the parent population and the way in which the ample subject were drawn are e en tial in evaluating limitation on gen eralizability in any epidemiological study This information hould be pro vided in the publi hed report of tudies The extent to which generalizability is requir d is dependent on the tate of knowledge at the time at an early tage of knowledge a mall tudy on a limited population may provide clues which can l e explored in sample from broader population to permit exten ion of the generalization

3 The fir t aim of epidemiological tudy is to identify character tic of in dividuals and of their environment (broadly defined environment includes all agents impinging on the individual) which are a ociated with the existence or occurrence of di ea e These a ocia tions can be tested for stati tical ig nificance by tandard technics and it is now generally under tood that the ac ceptance of the finding of significant a ociation does not imply the establish ment of a cause and effect relationship Neverthele the search for a ociations is a search for factors which may be etiologic in the di ease the degree of confidence in which the a ociations are held taking into account information from other sources such as hypotheses about mechanisms involved should point the way toward conclu ive tudies of etiology

4 In tudies of human populations it is rarely appropriate to tudy a single factor u ually multiple factor and as sociations are studied A number of probable factors in the etiology of cardio va cular di ea es have been identified in previous studies In the search for new factor those already implicated hould wherever po ible be ob erved and taken into account in the analysis of the new study Alternatively certain variables may be controlled by limit ing the study to group of per ons which are relatively homogeneous with re pect to these variable e g persons with specific age ex race occupational or other character tics

5 The ob ervational epidemiological study lacks two important elements of the clinical or laboratory experiment First no attempt is made to alter the character tics of the group under tu ly rather there is dependence on th so called experiment of opportunity which concomitants of variation in the ex ting environment (external or in ternal) of the individual are analy d in the ame fa hion as the sequela of ex perimentally introduced chang in controlled laboratory tuati becau e no attempt is m d pecific variables th of randomization of

viduals to treatment and control groups is missing from this type of epidemiological study.* For example in a study of the association of smoking with risk of coronary artery disease by analogy with the clinical trial smokers may be regarded as the treated group and non smokers as the control group. Failure to randomize places restriction on certain statistical generalizations and requires that they be considered as approximations to the experimental situation where true randomization is applied. On the other hand the attempt to control all relevant factors in the experimental situation may well result in the loss of information on important interrelationships because the range of environmental factors is artificially limited. This may constitute a severe limitation to generalization.†

B. *The Time Reference of Studies Retrospective and Prospective*

The pathologic changes involved in arteriosclerotic heart disease and hypertension develop over a period of years and appear to be influenced by host or environmental factors which exert their force over much of the lifetime of an individual prior to the time the diseases become clinically recognizable. Data pertaining to a substantial portion of the life span of the individual prior to identification of his disease are much more likely therefore *to yield information* of value than contemporary data alone. It is for this reason that time-span studies either retrospective or prospective are often regarded as superior to cross-sectional studies. In fact each of the three methods has both advantages and disadvantages which must be balanced in the individual instance.

The prospective and retrospective approaches will be considered first with the discussion of the cross-sectional study reserved for a later section (IC).

In the typical prospective study (which is frequently referred to as a longitudinal study or study of cohorts)‡ a population is selected for study without prior knowledge of the disease status of the individuals making up the population. Each individual is examined at the outset of the study and classified as diseased or free of disease. At the same time data on other individual characteristics which might possibly be related to risk of disease are secured and recorded. Those free of disease are regarded as the population at risk and are observed over some time period. At the end of the period the population at risk can be classified into two groups those who have developed manifest disease and those who remain free of disease. It is also possible to classify the population at risk into groupings on other factors (e.g. lipid levels, body fitness, dietary patterns) which characterized each individual at the time of entry into the study. If differences in incidence of disease are found in the various groupings on some classification

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* It is recognized that there is an area of experimental epidemiology which has many of the aspects of the clinical trial including randomization. This special type of study will not be discussed in this report.

† For more extended discussions of the points raised in this section and references to the literature see references 1 and 2.

‡ There is not full agreement on appropriate terminology for describing various types of studies. In this report prospective and longitudinal are used synonymously for studies in which groups are followed from the time of definition forward in time. The term "cohorts study" has been proposed to describe the prospective study in which specific individuals are followed. In contrast to an alternative type of longitudinal study in which successive samples of an originally defined group are studied rather than identical individuals. (This latter type of design has been discussed in reference 3 and is not further discussed in this report.) Since the term "cohort" in life table analysis implies a group of persons born in the same year whose subsequent mortality experience is described the term "cohorts study" would appear to be applicable to the type of longitudinal study where individuals of varying ages at entry to the study are followed in time.

the a ociation uggests the pre ence of an etiological factor *

In the typical retro pective study one group of individual is brought into the tudy because they have exhibited mani fest igns of di ea e A econd group of individual are elected for tudy who are free of di ea e Often the latter group are matched with the former with respect to a e ex or other factors Data are then ecured on other indivi dual characteri tics of the persons in the two groups in re pect to life ex perience *prior to development of* di ease or in the case of those free of di ea e prior to entry to the study As in the ca e of the pro pective tudy the characteri tics of the two groups are examined for differences which will uggest etiological factors †

There are many pos ible variations within the e two types of tudie but the important difference between the two is that in the prospective study data on the di ea ed are recorded before the criterion event (or diagnosi) and in the retro pective tudy after the cri terion event (though with re pect to a time period before the event) In prac tice nearly every pro pective tudy make u e of some retro pective data e g a lifetime hi tory of smoking ob tained at entry to the tudy but the important difference is that it i ecured before the occurence of the criterion event

The retro pective approach contains certain problems of sampling de ign which may be very difficult though not necessarily impo ible to overcome At any given point in time it may be ex tremely difficult to ecure a representa tive coronary population The ur vivor who are the only ones available for tudy may be quite different for example from those who died in their fir t attack If usual medical sources are u ed for the election of the cor onary population ome important groups of the population may be omit ted It i al o difficult to pecify the method of sampling for the election of the appropriate compari on group ‡

Another problem in the retro pective tudy i that the occurrence of the cri terion event may cau e the affected in dividual (or his phy ician or a family informant) to revi e the information that would have bi en pre ented in ad vance of the criterion event It is for this rea on that the burden of proof lies on the inve tigator in the retro pec tive tudy to demon trate (perhap by ancillary tudies) that the occurrence of the criterion event does not affect reporting of prior events

The kind of data available for retro spective studies are frequently not de termined by the investigator nor recorded with his purpo es in mind nor a ea ily subject to validation proced ures as are data recorded in a pro pec tive tudy Thus the study dependent on pa t ho pital record may encounter frequent gaps and hifts in recording method

The pro pective tudy encounters other and different ampling problems One of the chief of these i the prob lem of nonrespon e either in terms of refusal to participate in the initial ex amination or refu al to participate in the follow up examin ation The ex pen e of the pro pective study almost invariably limits the repre entativeness of the group which can be studied

There are certain ri ks of bias in the pro pective tudy in that the process of ob ervation may itself influence the rate of development of di ea e in the popula tion There e also the po ibility that early findings in the tudy will cau e bi ases in ub equent observation

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Descript on of thre pr pect ve tud in the dio a cular field will be f und in eference 4

† See eferenc 5 for descript on of a retro-pe tive tu dy f th s gen al type

‡ Fo e t nded d cus on f sampl ng p b l m see ref re e 6 a d

Studies designed to assess these risks are needed.

The cost of maintaining a prospective study in operation for a period of time long enough to provide useful data and the problem of maintaining continuity of personnel are undoubtedly severe handicaps to successful prosecution.

Both the prospective and the retrospective study are observational studies and neither can demonstrate causation in the same sense as an experimental study. The prospective study is theoretically superior to the retrospective study in sample design and in protection against the risk of bias in a posteriori observation and recording of data and for these reasons it has been preferred by statisticians. On the other hand, skilled investigators have developed methods for protecting against many of the dangers of the retrospective study.* If these risks can be minimized by appropriate safeguards the retrospective study will be attractive because of sizable savings in both the length of time required to produce significant findings and in cost.

Prospective studies can in some instances achieve some of the economies usually attributed to retrospective studies by delaying processing of data until its pertinence has been established. For example, in a prospective study of total serum cholesterol and coronary heart disease, data for the entire study population could be stored and cholesterol level tested only for subjects in whom the disease occurs plus a relatively small sample of the vast majority of subjects in whom it does not occur.

In balance, at an early stage of knowledge the retrospective study is a relatively quick and inexpensive but insecure method for gaining insight into the etiology of disease. If the findings of such a study are challenged on the ground outlined above, the challenge can only be answered by conducting a prospective study. But as in the case of the smoking and lung cancer controversy it is clear that even the prospective study is not immune to challenge when offered as proof for causal relation.

C. Cross-Sectional Studies

In the cross-sectional study in contrast to the time-span studies the analysis is based on comparison of observations on groups of individuals at a given point in time. It is useful to consider two types of cross-sectional studies.

In the first type a group of persons with known disease are available for study and a group of persons free of the disease are elected for comparison. Each individual is thus characterized as to presence or absence of disease and in addition by contemporary observations on other factors believed to be relevant to the disease process. The interpretation of the results must necessarily be based on the assumption that the differences observed between the two groups are similar to those which would have been found if it had been possible to observe the groups before the criterion event.

This type of study differs from the retrospective study previously described *only in the fact that data are secured* by contemporary observation and not by recall. While the cross-section study is thus protected against the possible effects of the criterion event on recall, this protection is secured at the expense of omitting data on the period prior to the criterion event. The cross-sectional study is subject to the possibility of bias if the disease group has become of the occurrence of the disease shifted its position with respect to pre-disease characteristics. Shifts in characteristics may be physiological sequelae of the attack itself or a result of subsequent treatment. Thus certain lipid

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*Reference 5 provides examples of several methods for testing validity of retrospective data.

level or blood pressure or weight for example might differ from those which existed before overt disease occurred The cross sectional study is subject to the same problems of sampling as the retrospective study in that those in the disease group represent only the survivors of some larger group which had experienced disease The relatively large group of coronary cases which die suddenly in the first attack for example are rarely included in hospital series If it should be shown that the sudden death group differed significantly from other coronary cases then a study based on survivors only would yield a biased finding Also as with the retrospective study it is difficult to specify what non coronary group is appropriate for comparison because of uncertainty concerning the original disease free population from which the coronary group arose

In a second type of cross sectional study groups are characterized as to disease prevalence (or incidence) rates and simultaneously characterized in terms of group averages with respect to other factors eg proportion of caloric intake in the form of fats of various types If differences in prevalence rates are found to be associated with group differences in other factors it may be inferred that the factors have etiological significance Groups may be chosen on many different grounds For example when it is found that groups selected for study on the basis of age and sex show different prevalence rates of disease the inference is made that these factors are significant in assessing risk of disease It is clear from this trivial example that analysis at this level will not throw much light on differentials in risk within age sex groups unless individuals can be further subclassified both with respect to disease status and other characteristics More frequently this approach is used in comparing disease prevalence in groups differing in occupation or in geographic location (with accompanying racial cultural or other difference) It is clearly profitable to seek groups differing widely in disease prevalence and to explore other factors characterizing these groups with the hope that factors which differentiate the groups may provide leads for further investigation Frequently a direct interpretation will be difficult because of the confounding of many factors *

D *Problems of Sampling Selection of Comparison Groups*

In previous sections a number of problems of sampling have been touched upon It has been pointed out that no population in general or whole in the sense of not having its own peculiar characteristics reflecting factors which may be of importance to the study of disease such as its prior mortality experience ethnic origin age and sex composition and a wide variety of environmental circumstances Thus the most defensible sampling method insure only that the sample statistics will provide estimate of the parameters of the population sampled within specifiable probability limits It seems probable that studies of cardiovascular disease of the depth required by the present state of knowledge will continue to be limited as to scope in both time and area coverage because of cost and limited availability of trained personnel Under these circumstances the repetition of studies under comparable conditions with well designed samples and in different places will provide reinforcement of similar findings even though there may be no statistical method for making a probability statement about the combined results

In a number of international cross

* The approach sometimes termed geographical pathology or human ecology has been discussed in some detail in publications which became available subsequent to the conference see reference 8

ectional tudies now being carried out the group elected for tudy have been cho en by a method which has been re ferred to as chunk ampling* The chunk may be a circum cribed occupa tional group (such as firemen in a given locality) or the residents of a small villa_e Within the chunk an attempt is made to ecure 100 per cent coverage in order to avoid the bias of individual election Comparisons are then made between imilar group in different countrie in order to draw in ferences about po ible cau al factors when differences in disea e prevalence are found This approach ha many advantage and permits the carrying out of tudies in area where more ex ten ive samplin_ would not be fea ible It mu t be reco_nized however that there are elective factors in affiliation of individual with occupational group and that the e may vary from area to area The utility of the chunk am pling approach will be increa ed as more comparative information i made avail able not only concerning variations between chunks in different countries but al o between individual chunks within a country and the remainder of the population of that country Results from tudies of the type mu t be in terpreted in terms of pre ent limitations on knowled_e of the representativene s of the group

In the di cu ion of the typical retro spective and cro ectional tudies it was pointed out that there are erious problem of amp ling in the election of the appropriate free of di ea e group for comparison with the di ea e group These problem are of ufficient im portance to warrant further elaboration here In the traditional design of the experimental tudy patients are a signed to treatment and control groups at random before the experiment and it is thi random a ignment which makes pre ently available tati tical theory ap propriate for analy i In the long tudinal tudy the treatment are no a igned at random since other indi vidual nonrandom element come into play in the placement of individual into treatment groups on a facto uch as for example body fatnes However in the longitudinal tudy the population out of which the di ea e group originated i pecified at the on et of the tudy and can be cla ified on a ingle characteri tic uch a degree of body fatnes from the beginning of th ob ervation Under these circum tance it i appropriate to test the a ociation between body fatness and ri k of di ea e by testin_ whether the new ca es of di ea e are di tributed among the various body fatne grouping in a manner compatible with the a umption that there i only random variation from a uniform average ri k in all group —which upport the deci ion of no a ociation Alternatively if the distribution of new ca es among the variou body groupin_s i uch that it would have been very unlikely to occur if there were only random varia tion from a uniform average ri k then the deci ion of ignificant a ociation is upported (It has already been re marked that a ociation doe not neces arily upport the inference of cau al connection)

In the type of study where a compari on group of free of di ea e per ons are elected for contra t with the di ea e group there is neither the element of randomization in a signment of treat ment found in the ideal experiment nor is there the certain knowledge that the per ons free of di ea e at conclu ion of follow up are the remainder of the original population from which the new disea e cases came—the situation which makes permi ible the type of tati tical te t de cribed above in the typical longitudinal study

There are in fact no logically de

*For a di u ion of this approa h and gen eral pro lems in ur ey ee reference 9

fen ible rules which can be pecified for the election of a compari on group in the type of retro pective or cro s- ec tional tudy where independent election of di ea ed and free-of di ea e groups i necessary What can be pecified is that the two groups should be as much alike as possible with respect to factors which are known in advance to differ entiate the two groups * The difficulty is to in ure that the election process does not permit the introduction of other factors which would differentiate the two groups and yet be unrelated to the di ea e proce s it elf Thu when tudie of this type are undertaken a large part of the protection again t mis leading interpretations mu t rest on that part of the kill of the experienced in vestigator—medical or stati tical—which i art rather than cience

E *The Problem of Nonresponse*

General population studies in which clinical methods have been u ed for diagno is of disea e have rarely ecured participation in American populations from more than three fourths of the de ignated ample Presently available technic including u e of mobile ex amining units conveniently located ap parently are not adequate to rai e the re pon e rate above this level † Incom plete re pon e introduces the trong po ibility of bias in result but the nature of thi bias has not been ade quately studied becau e suitable means for doing so have not been found There i urgent need for further methodologi cal tudy in this area It i al o im portant that data on respon e rate be pub li hed in detail with the report of each study

The completene-s of examinations in terms of procedures to which the sub ject is a ked to ubmit and the time required to carry them out appears to discourage participation The desira bility of completeness of information must therefore be balanced in any tudy again t the de irability of a high rate of respon e

In longitudinal tudies where the major compari ons are among groups of persons who actually participate initial nonre pon e is less erious than in cro s ectional tudie provided that virtually complete follow up of the initially respondent group can be e cured A high drop out rate ub-equent to initial respon e could however be related to health tatu and thus intro duce erious bia Fortunately it has been demon trated in everal longi tudinal studies that while it was im po ible to secure complete re ponse from the original sample it ha been much les difficult to secure reexamina tion on the original re pondent

Four types of information are u eful in evaluating the effect of nonre pon e in both longitudinal and cro sectional tudies

1 I format on about th d idual h alth status a reported b h m in hom interview by a lay interviewer—obtai ed prior to the inv tation t pa t pate in med cal examination procedure

2 Mort l ty data and data f m ho pitals n l phy icians on no pa ti ipants for com parison with imilar data for participant

3 W th the p rt p t g g oup an analy is of h alth tatus amon resp ndent cl fied a o d n to th am unt and type of effort requ ed to e pa t pat on

4 Special sample studies of nonrespond nt h l y u g som mi mal cl ni al ob rvat o in the h me.

II Measurement Problems

A *Definition of the Disease Being Studied*

Our concept of disea e changes when method available for diagno ing

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S m metho l for tatist al h ndl f d ta wh e matche l control" are u e i tudi of thi type a e described in r fer enc 10

† P el m nary report from the N t onal H alth Su ey ha e ind cated that it may b pos il le to ecure h he ponse rat s in om a e C ntinue l methodol al ve ti gati n i b g nde taken

disease change The decision to make an epidemiological tudy ordinarily implies that there are available sufficiently precise method of diagnosis to permit the identification of case of disease under tudy In this respect the tudy of hypertensive and atherosclerotic cardiovascular disease is beset with serious problems for lack of objective criteria for identification The evaluation of blood pressure level is difficult enough But even granting a reliable pressure evaluation there appears to be little unanimity as to the other measurable characteristics which should be assessed in order to classify a person into the groupings hypertensive disease or not hypertensive disease Similarly with respect to coronary artery disease while the evaluation of the frank coronary attack can undoubtedly be made with relative precision there appear to be no adequate method for estimating the extent of advancement of the underlying atherosclerotic process In longitudinal tudies as well as in clinical experience a significant proportion of subjects found to experience frank coronary event have been classified as apparently free of disease at examination not long before the event Cross-sectional studies miss such cases entirely

The existence of this problem has led to what might be called the Substitution Game in which blood pressure level is substituted for hypertensive disease or serum cholesterol level for coronary artery disease It would appear that these substitutes can at best be only crude indexes of the diseases which it is desired to tudy and their uncritical use may obscure important relationships*

It seems clear that better methods of diagnosis adaptable to the needs of large scale studies need to be developed In any event the methods employed in current studies should be explicitly described and knowledge of their limitation should be taken into account in interpreting results

B Validity of Measurements

A measurement procedure is valid if it measures what it purports to measure a procedure is reliable if it gives the same results when used repeatedly in the same situation (i.e. when it is reproducible) A measurement procedure may be valid even though its reliability is low a highly reliable (or reproducible) procedure may be of low validity

The validity of a measurement whether of the existence of disease or of some characteristic of an individual (physiological biochemical environmental and so forth) is relative validity is often judged qualitatively but should be quantified whenever possible For example a given ponderal index based on some ratio between weight and height may be considered a good index of fatness but can be checked against the more nearly exact measure of underwater weighing Two-stage sampling is useful in checking the validity of a convenient relatively inexact test applied to an entire study group by subsequently applying a finer but less convenient measure to a subsample

C Reliability (Reproducibility) of Measurements

There are two factors which affect reproducibility of biological measurements—variability in the measurement process itself and individual biological variability The former can often be controlled to some extent provided that the investigator is forewarned of its existence by routine reproducibility studies An investigator can rarely control individual biological variability

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* It is not intended to imply that the descriptive epidemiology of blood pressure or cholesterol levels while valuable is unprofitable At the present stage of knowledge such studies may make valuable contributions to the understanding of disease

he can only reckon with it in his analy is but again only if he has ade quately evaluated it

Every tudy hould make some pro vi ion for tests of reproducibility of at lea t selected types of mea urements on amples of subject throughout the cour e of the tudy The essential factor in such test is the independent applica tion by two or more person of the ame procedure to the same object of study whether the object of tudy be a pecimen of erum an x ray film or a ubject s de cription of his symptoms With advance planning incorporation of such tests is fea ible though it is recognized that tests of particular kinds of measurements are time con uming co tly and not without technical prob lems in execution An attitude of un questioning confidence in procedures cu tomarily u ed may be a major obstacle It would be desirable to estab li h agreed upon tolerance levels of measurement error for tho e measures common to epidemiological studies in the cardiovascular field

Individual biological variability is much more difficult to evaluate than imple laboratory reproducibility yet it may be much more important in intra individual compari ons in longitudinal studies There is need for more com plete documentation of individual vari ability for many widely u ed mea ures and in some in tances this will require the etting up of pecial tudies The committee notes that other committees of the conference have considered this problem in their report

D *Minimum Base Line Measures and Standard Methods of Presentation*

The committee believes that the epi demiological tudy of cardiova cular di ea e will be more productive if step are taken to ecure a greater degree of comparability between the studies which are being carried out by investigators in different population groups One re quirement for comparability is agree ment among inve tigators to include in each study a pecified minimum et of mea urements to be carried out under tandard pecifications A econd re quirement is that publi hed reports of studies pre ent the e minimum data in ome standard format (Alternatively it could be agreed that standard tabular material be deposited with the Ameri can Documentation In titute with the depo it noted in the published report) The committee believes that the progress made by the other committees of the conference toward agreement on stand ard patterns in several areas of inve ti gation is evidence that these aims are achievable and that they can be achieved without putting any undue burden on the individual study or re tricting the freedom of the individual inve tigator The committee recom mends that the sponsoring organizations con ider setting up a continuing group to make recommendations in these areas and to subject the e recommendations to periodic review and revi ion as required by changing development in the field

REFERENCES

COMMITTEE ON CRITERIA FOR DIAGNOSIS OF DISEASE AND CLINICAL EVALUATION

Joseph T Doyle MD Chairman

SUBCOMMITTEES ON CLINICAL EVALUATION BLOOD PRESSURE MEASUREMENT AND ECG INTERPRETATION

This report summarizes the deliberations of three subcommittees which considered the definition and the clinical evaluation of ischemic heart disease and of hypertensive disease the use of electrocardiography in epidemiologic studies and the measurement of arterial blood pressure An attempt is made to offer realistic recommendations concerning diagnostic methods The numerous lacunae in our knowledge of degenerative heart disease are urgent indications for further research The committee feels that epidemiologic surveys offer an unusually good opportunity for research in many levels and strongly recommend that such opportunities be exploited

Epidemiologic studies are concerned with the incidence and prevalence of diseases in population groups rather than in individuals The occurrence of disease is then correlated with other characteristics of the population What is needed is a reliable index of disease which will identify the same proportion of cases of disease in various populations rather than a method of locating every single case of disease An objective method such as electrocardiography which is relatively free from falsifying factors can give a better index of disease rates than the subjective manifestations of the anginal syndrome which may identify larger numbers of cases but are affected by individual differences unrelated to the disease being studied

Ischemic Heart Disease

Definition—Consistent with the recommendation of the World Health Organization Study Group on Atherosclerosis and Ischemic Heart Disease the term ischemic heart disease will be used The definition is as follows

> Ischemic heart disease is defined as that cardiac disability acute and chronic arising from reduction or arrest of blood supply to the myocardium in association with disease processes in the coronary arterial system The two main pathological processes involved are (a) atherosclerosis of and (b) thrombosis in these vessels The same processes may be responsible for atherosclerotic and ischemic cerebral and peripheral vascular disease [1]

The classification recommended by the WHO Expert Committee on Cardiovascular Disease and Hypertension is endorsed with a number of modifications which are contained in the following extract The principal manifestations and clinical syndromes of ischemic heart disease are as follows

I Myocardial Infarction

(a) Definite Myocardial Infarction —A disease due to obstruction of the coronary circulation and causing necrosis of a macroscopic circumscribed area of myocardium Such an area will if death does not ensue undergo fibrosis The well known signs and symptoms of acute myocardial infarction will rarely be encountered in field studies The diagnosis of previous acute myocardial

infarction is based on these two features

(1) History—A clear history given by the patient of the sudden (less often of the gradual) onset of severe chest pain or discomfort usually at rest and located as in anginal syndrome (2a below) frequently associated with vasomotor collapse and often requiring prolonged bedrest If the patient was hospitalized the information obtained from hospital records should be separately entered so as not to bias comparisons with results from cases where such information cannot be obtained

(2) Electrocardiogram — Serial electrocardiograms taken during the acute phase of myocardial infarction are usually conclusive evidence of the lesion The electrocardiogram often reveals stigmata strongly suggestive of or diagnostic of old myocardial infarction An example of some tentative criteria for the recognition of old myocardial infarction is given in Appendix A Technical aspects of electrocardiography are discussed in a subsequent section of this report

(b) Possible Myocardial Infarction —The history is not as clear cut as in definite myocardial infarction but includes pain or discomfort similar in *location but more intense and/or of* longer duration than in anginal syndrome (see 2 below) The electrocardiogram is not normal but is not typical of definite myocardial infarction

2 Anginal Syndrome—It has been argued against the use of this syndrome that it is entirely subjective and depends on the observed and the observer It is felt however that the manner in which the patient describes anginal pain is so characteristic that it cannot be considered only subjective and warrants the diagnosis of anginal syndrome as a subclassification of ischemic heart disease Due care must be taken to recognize the exclusion categories (see 2c below)

(a) Definite Anginal Syndrome—A discomfort or pain occurring across both sides of *the anterior chest wall* or located centrally in the sternal region brought on by effort (e g exercise emotion exposure to cold and wind) It may radiate to the left arm or both arms the shoulders the neck or jaw It is spontaneously described as pressing tight heavy constricting or crushing or as numbing or burning It is usually relieved within a few minutes after cessation of effort or of taking sublingual nitroglycerine Cases of angina at rest will rarely be encountered in field studies

(b) Possible Anginal Syndrome—

(i) Discomfort or pain as in definite anginal syndrome but beginning in any of the sites of radiation mentioned.

(ii) Discomfort or pain as in definite anginal syndrome but commencing in the left or right anterior chest or in the epigastrium

(iii) Discomfort or pain as in definite anginal syndrome which may subside despite continued effort

(c) Exclusion Categories—

(i) Discomfort or pain as described above occurring after cessation of effort as contrasted with discomfort occurring during effort (e g in anxiety states)

(ii) Discomfort or pain as described above occurring only in relation to meals and posture (e g hiatus hernia)

(iii) Discomfort or pain as described above but related only to special movements and positions of the body (e g arthritis fibrositis)

(iv) Stabbing or lancinating pain in the region of the left breast (e g in anxiety states)

(v) Localized or general chest and/or arm discomfort or pain due to thoracic outlet or hyperabduction syndrome

3 Sudden Death—At the present *time there is insufficient quantitative* evidence to justify the use of sudden death as an index of the frequency of ischemic heart disease Except for special studies this term should be used in the sense of instantaneous death Sudden death should become a useful index if quantitative estimates can be obtained in unselected populations of the relative numbers of deaths due to *ischemic heart disease and to other* vascular catastrophes This problem is considered in detail in the Report of the Subcommittee on Morphology

1 Congestive Heart Failure—A complex syndrome manifested by dyspnea diminished exercise tolerance pulmonary congestion water and salt retention hypervolemia venous hypertension planchnic congestion and peripheral dependent edema In the absence of other nosologic factors it is often assumed that congestive heart failure is due to diffuse myocardial damage caused by coronary artery occlusion This assumption is unfounded Chronic heart failure cannot therefore be considered a reliable index of ischemic heart disease

The following comments were made by the committee on diagnostic method

1 History—*In the absence of* any other information it must be assumed that a history of anginal syndrome or past myocardial infarction can be reliably obtained only by a physician There is no information concerning the reproducibility or the reliability of such histories taken by physicians of varying levels of training and experience It must also be conceded that the accuracy of a history of ischemic heart disease obtained by a personally trained lay interviewer has never been evaluated This possibility deserves intensive investigation for use in epidemiological studies There is sufficient experience with self administered questionnaires to condemn their use in field studies[3]

2 Physical Examination—There are no readily *discernible abnormalities* characteristic of ischemic heart disease It is *however possible to detect evi*dence of atherosclerotic obliteration of *other vascular territories such as in* the brain retinal vessels and the lower extremities This *information* may be epidemiologically just as important as evidence of ischemic heart disease

3 Electrocardiogram—It is a truism that the electrocardiogram does not identify atherosclerosis but only its myocardial ischemic *complication* A majority of individuals with the anginal syndrome exhibit normal resting electrocardiograms[4] An unknown number of individuals recover from acute myocardial infarction with no residual electrocardiographic abnormalities or with intraventricular conduction defects not usually ascribed to myocardial infarction[5]

There is interesting indication that an abnormal electrocardiographic response to stress is valuable evidence of ischemic *heart disease If* time and budget permit and if adequate medical *supervision is available it is suggested* that an electrocardiographic stress test *be incorporated in some epidemiological* studies It must be recognized that such tests carry a *small but definite risk* The diagnostic criteria of an abnormal electrocardiographic response to exercise proposed by Robb and Mattingly are endorsed[6]

Hypertensive Disease

The following appears to be a satisfactory definition of the hypertensive process

The term hypertensive disease is synonymous with essential hypertension and should properly be restricted to designate the as yet unidentified physiological disturbance (or disturbances) characteristic of this disease and which lead ultimately to elevation of diastolic and systolic blood pressures Anatomical changes in the vascular tree and functional impairment of the involved tissue Hypertension is the earliest clinically recognizable disturbance and results from constriction of the peripheral arterioles this constriction leading to an increase in the total effective peripheral resistance and hence to elevation of diastolic and systolic blood pressures Hypertensive disease is considered to be a clinical entity on which an unknown pressor mechanism initiates arteriolar vasoconstriction elevated blood pressure and vascular sequelae Hypertension as such like arteriolar changes is considered to be a sequela appearing during the progressive development of the disease[7]

Blood Pressure Criteria—It is advocated that cumulative frequency distributions and curves be used to report the

level of arterial blood pressure found in any defined population these provide the best way of comparing populations It is recognized that clinical usage demand arbitrary criteria of normal and of abnormal arterial blood pressure The following criteria are therefore suggested as a supplement to but not as a substitute for cumulative frequency curves The proposed numerical values can obviously be adjusted to suit the needs of any particular investigator

(a) Normotension—Systolic blood pressure below 110 mm Hg *and* diastolic blood pressure below 90 mm Hg i e *both below*

(b) Hypertension—Systolic blood pressure 160 mm Hg or over or diastolic blood pressure 95 mm Hg or over i e either one or both at or above the specified level

(i) Systolic Hypertension—Systolic blood pressure 160 mm Hg or over *and* diastolic blood pressure *under* 90 mm Hg

(ii) Diastolic Hypertension—Systolic blood pressure *under* 140 mm Hg and diastolic blood pressure 95 mm Hg or more

(c) Borderline Hypertension—This is *the residual category* i e *the systolic* blood pressure is below 160 mm Hg *and* the diastolic blood pressure is below 95 mm Hg but they are not simultaneously below both 110 mm Hg systolic and 90 mm Hg diastolic Note that the diagnosis of hypertension is based on either or criteria while normotension requires that both the systolic and the diastolic reading be below the cutting points

When multiple determinations are made the assignment should be based on the first determination or on the mean [9]

The following general statements can be made concerning *clinical evaluation* of participants in epidemiological studies

1 Hypertensive Disease Uncomplicated—As the term implies consistently elevated arterial blood pressure is the only deviation from normal No symptoms characterize this phase Complete clinical evaluation requires the exclusion of *visceral involvement and of* causes of secondary hypertension Since secondary hypertension is rare it would seem unnecessary in epidemiological studies to make special efforts to identify such cases

2 Hypertensive Disease Complicated—This term implies visceral involvement which depending on the degree of organ compensation may or may not be characterized by symptoms The vascular 'territories' most commonly affected by the hypertensive process are in the heart the brain and the kidneys Marked elevations of the diastolic blood pressure accelerate and aggravate atherosclerosis [8] The definition of hypertensive heart disease is inevitably circular since it is dependent on the demonstration of what is considered to be an abnormally elevated blood pressure associated with signs and ultimately symptoms of an increased left ventricular work load In many instances the visceral complications of *hypertensive disease may be due to* ischemia consequent to atherosclerotic thrombotic vascular occlusion The following clinical and laboratory procedures are suggested for field use

(a) Heart—History and physical signs of (paroxysmal) left ventricular failure Radiologic evidence of early left ventricular enlargement is notoriously unreliable Electrocardiographic evidence of early left ventricular enlargement is likewise unreliable Large QRS voltages in youth and early adulthood cannot be accepted as testimony of left ventricular enlargement. There is poor correlation between *the x-ray and the electrocardiogram in* early left ventricular enlargement

(b) Brain—History of or neurologic residua of a previous cerebrovascular accident. History of hypertensive encephalopathy Retinopathy fundoscopy is extremely helpful in the field and should at least distinguish normal or mildly abnormal eyegrounds from grossly abnormal employing the Keith Wagener classification [10] Under some circu-

stances it may be possible to take fundal photographs as an objective record

(c) Kidney.—There are no satisfactory bedside methods for estimating renal function. If orthostatic proteinuria be excluded, proteinuria is reliable evidence of renal functional impairment. Microscopic examination of the centrifuged urinary sediment is desirable. Cylindruria may be taken as evidence of renal tubular damage. Pyuria in the male is prima facie evidence of genitourinary infection.

3. The Prehypertensive State.—The existence of this phase is theoretical. There is no evidence that a labile arterial blood pressure necessarily precedes later hypertensive disease.[11] Tests for vascular hyperreactivity such as the cold pressor test are of no particular diagnostic value and are of unknown prognostic significance due to lack of prolonged follow-up data.[12]

Notes on Technical Methods

1. Measurement of the Arterial Blood Pressure

Instrumentation.—The Recommendations for Human Blood Pressure Determination by Sphygmomanometer sponsored by the American Heart Association are strongly endorsed[13] with the exceptions noted below.

It is felt that the following items merit emphasis. It is recommended that a cuff 12 to 14 cm. in width be used. The cuff should be so designed that closure and inflation will exert uniform tension over the whole width of the cuff. Where large numbers of measurements are to be made in a short time consideration should be given to the use of a pressure reservoir to inflate the cuff. The mercury manometer is the standard of calibration. The zero should be clearly visible, the upper end of the glass tube should be freely vented. Aneroid manometers are acceptable if checked frequently (every few days) against a mercury column. The tendency of observers to round off manometric reading is recognized. It is suggested, nonetheless, that the observer read the scale to the nearest even number. Objective automatic methods of measuring and recording the arterial blood pressure should be developed within current technical capability and are highly desirable to avoid the problem of observer bias. Despite the official recommendation that the arterial diastolic pressure be taken at the point of disappearance of the Korotkow sound, there is substantial evidence that the point at which the Korotkow sound becomes muffled may correspond more accurately with the true diastolic pressure.[14-16] It is therefore recommended that both points be routinely recorded. For the present the point of disappearance of Korotkow sounds should be used as the diastolic pressure for statistical purposes.

The Observer.—It is self-evident that if the auscultatory method of sphygmomanometry be used the observer must have adequate hearing. It is suggested that in epidemiological studies the observer should present a normal complete audiogram as a preliminary qualification. An acoustically acceptable stethoscope should be used. It would be highly desirable for the examiners in all population studies to practice together on the same subject until a satisfactory uniformity of blood pressure measurement had been achieved. It would likewise be highly desirable for similar inter-study comparisons to be made. To both these ends it is hoped that audiovisual training devices may soon be fabricated. The clinically traditional use of cutoff points to discriminate between normal and abnormal level of blood pressure inevitably creates observer bias as evidenced by anomalies in life insurance statistics and the universal tendency of numerical values for the diastolic blood pressure in particular to cluster at certain points.[17] The problem is so acute that serious consideration might

be given to the use of offset manometer scales to give a purious reading later decoded by the statistician Provision should be incorporated in all studies to code the observer so that the source of possible systematic deviations may be identified Since however the level of the arterial blood pressure may normally fluctuate widely [18] since almost all proposed criteria distinguish between diastolic normotension and diastolic hypertension on differences of only a few mm Hg since as previously noted the indirect measurement of diastolic blood pressure is uncertain unreliable and subjective and since there is no predictable association between the level of the arterial blood pressure and the presence of vascular damage the abandonment of arbitrary and rigid cutoff points to discriminate between normal and abnormal levels of arterial blood pressure is advocated It is felt that proper training and sound motivation are more important than the professional background of the individual who measures arterial blood pressure in population surveys

The Observed—It is probable that the casual blood pressure is most often measured with the subject in the seated position The arm must be at the same level as the heart There may be some advantage to measuring the blood pressure when the subject is supine since the arm is then at heart level and orthostatic hypotensive influences often exaggerated by antipressor and other drugs are abolished The diastolic pressure is less affected by changes in posture The systolic pressure may however be considerably affected by change in posture so that five minutes should elapse before it is measured [19] More comparative measurements of the arterial blood pressure in the supine sitting and even standing positions are required The minimum clinical data that should be recorded include the sex age height and weight and pulse rate of the subject Most hypertensives under treatment seem to be ignorant of the exact nature of their medication It seems nonetheless desirable to inquire of all subjects whether medication is being taken and to record whatever information is elicited The extent to which obesity of the upper arm may invalidate the indirect measurement of the arterial blood pressure is not completely known For this reason it would be worth while when feasible to make a comparative measurement of blood pressure in the forearm [20] [21] No definitive statement is possible on the optimal number of blood pressure measurements to be taken There is some evidence that when taken in rapid (30 second) sequence there is a successive decline of the second and third readings and that the third reading is fairly representative of those made subsequently [22] When multiple measurement of the arterial blood pressure show reasonable consistency the use of average values for statistical purposes is probably valid

II Electrocardiography

The Electrocardiogram—The electrocardiogram is an objective record of bioelectrical phenomena Strictly speaking anatomic inferences should not be based on this record Practically the diagnostic interpretation should be made only after collation of all clinical data

The ECG plays a small and uncertain role in epidemiologic studies of cardiovascular disease For example in atherosclerosis it will confidently identify only that small per cent of cases of coronary artery atherosclerosis where frank myocardial infarction has taken place Criteria for identifying normal from abnormal QRS items are reasonably reliable in many instances with the notable exception of QRS criteria for left ventricular hypertrophy S T and T criteria for normal and abnormal are much less reliably known The

committee is of the opinion that while large ECG surveys may usefully lend themselves to identifying the "normal" versus "abnormal" ECG, they do not lend themselves reliably to identifying specific disease. Furthermore, while criteria for the normal ECG are reasonably reliable in the age range 10-60 years, other age groups have not yet been adequately studied in this regard.

Direct writing electrocardiographs are suitable for population surveys but should be frequently checked to insure the accuracy of paper speed and of calibration voltage, stylus cleanline, centering and excursion, vacuum tube stability, and so forth. Standard electrode jelly or paste should be used as the electrolytic contact agent, although plastic electrode jelly is acceptable.

Lead Selection—Informal polls indicate that electrocardiographers consider the 12 lead (three bipolar and three unipolar limb leads and six or seven precordial V leads) electrocardiogram the diagnostic standard. There is, however, no evidence that the 12 lead electrocardiogram is essential to adequate diagnosis. No more information is contained in unipolar than in bipolar limb leads or vice versa. Conventional precordial lead placement is arbitrary and presents no intrinsic merit save that of general usage. Indeed, the placement of precordial leads at the three, four and five positions is subject to anatomical variation and particularly to technician error. The potential gain in *ease, speed and money commend the study of the value of limited numbers of electrocardiographic leads.*[?]

The Electrocardiographer—Conventional training in electrocardiographic interpretation requires an apprenticeship of a year, while competence can be maintained only by continuing experience. Relatively little is known on either an individual or a group basis of the accuracy, reproducibility and reliability of electrocardiographic interpretation. If large population studies are to be conducted these questions must be answered. In addition, means must be devised to cope with the enormous numbers of electrocardiograms taken in such studies. Unquestionably, a competent electrocardiographer could rapidly and accurately sort electrocardiograms into normal, borderline and abnormal groups up to the limit imposed by fatigue. It is felt that intensive investigation should be made of the problem of developing generally acceptable criteria of electrocardiographic interpretation simple enough but yet sufficiently accurate to be used effectively by a physician or by a technician not specially trained in electrocardiography. The use of simplified improved lead systems is particularly germane to this problem. If, as seems likely, electronic computers come to be used more commonly in biological investigation, the development of suitable electrocardiographic diagnostic criteria will be essential to intelligent programming of such instruments. The Laboratory of Physiological Hygiene of the University of Minnesota, with these purposes in view, has devised a set of criteria for the electrocardiographic diagnosis of myocardial infarction (Appendix A).

REFERENCES

1. [illegible] 1959.
2. [illegible] 168, 1959.
3. [illegible]
4. [illegible] 47:4 25-3 (Apr.) [illegible]
5. [illegible] 7:43-448 (Feb.) 1958.
6. [illegible] Double [illegible] Two-Step [illegible]

APPENDIX A

Excerpt from
Classification of the Electrocardiogram for Epidemiological Studies

This excerpt is presented as an example of the kind of criteria for old myocardial infarction which can be constructed based on electrocardiographic surveys of large groups of persons. The examples pertain to resting electrocardiograms taken in the supine position on adults under the age of seventy. Further information about the complete classification can be obtained from the author.

A. QRS Criteria, Type I (Myocardial Infarction)
(Q must be 1 mm or more to be designated as such.)

1. Q/R ratio of ⅓ or more in any of lead I, II, V₂, V₃, V₄, V₅, V₆, or if the transition zone is to the left of V₅ in lead V.
2. Q wave duration of 0.04 second or longer in any of lead I, II, V, V₂, V₃, V₄, V₅, and if R is plus 3 mm or more in all.
3. Q wave duration of 0.05 second or longer in lead III or if R is plus 3 mm or more in aVF. (Some Q must be present in VF.)
4. QS pattern (absent R wave) in any of lead V, through V₆ when an R wave is present in the adjacent precordial lead to the right.

B. QRS Criteria, Type II
(Q must be 1 mm or more to be designated as such.)

1. Q/R ratio of ¼ to ⅓ in any of leads I, II, V₂, V₆, or if right ventricular hypertrophy is not present in lead V₁.

Prepared by Henry Blackburn, Ernest Simonson, Ancel Keys, et al. Laboratory of Physiological Hygiene, University of Minnesota. The complete criteria include most electrocardiographical normalities of importance for epidemiological studies.

2. Q wave duration of 0.03 to 0.04 second (in any of lead I II V_4 V_5 and if R is plus 3 mm or more in aVL)
3. Q wave duration 0.01 to 0.03 second in leads III or aVF (Some Q must be present in aVL)
4. Q amplitude of 5 mm or greater in leads III or aVF when an R wave is present
5. QS pattern in V_4 V_5 in the absence of left bundle branch block and left ventricular hypertrophy

SUBCOMMITTEE ON MORPHOLOGY

David W Spain MD Chairman

Introduction

This report presents the combined effort of the committee and the conclusions represent complete agreement among the members of the committee It is particularly worthy of mention that basic agreement was rapidly reached in all major aspects of this report Comparison with the conclusions reached by the WHO Study Group on Atherosclerosis also reveal major similarities with this committee conclusion The recognized difficulty in epidemiologic studies on coronary atherosclerosis in live population groups is the inability to obtain precise measurements of the degree of atherosclerosis that may be present in any of the individuals studied In autopsy studies this difficulty is to a great extent eliminated but studies on autopsy populations suffer from lack of ability to properly generalize the findings to the population as a whole Nevertheless it is believed if comparable post mortem methods are used in different areas of the world a valuable contribution may be made to further the understanding of the pathogenesis of this disease

Definitions

The definition of the atherosclerotic lesions to be measured was similar to that agreed upon by the WHO Study Group in 1958 This definition is as follows

> Atherosclerosis is a variable combination of changes of the intima of arteries consisting of focal accumulations of lipid complex carbohydrates blood and blood products fibrous tissue and calcium deposit and associated with medial change"

The lesions to be considered within this classification may be subdivided or classified in several different ways The manner of subclassification is less important than the preciseness and clarity of the definitions Some will classify the various lesions into fatty or lipid streaks fibrous plaques atheroma and complicated lesions The complications include hemorrhage into the lesion superimposed thrombi ulceration and calcification Others suggest that the lesions be divided into lipid streaks fibrous plaques complicated lesions and calcifications definitions of these classes of lesions are given in Appendix A Listing of these lesions in the above order does not necessarily imply any exact biological sequential relationship It is also understood that the term fibrous plaque does not preclude the presence of lipid complexes within its depths The importance of defining and

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Classification of Atherosclerotic Lesions (Report of a Study Group) WHO Tech Rep Ser No 143 1958

ubclassifying the e le ions resides in the fact that in any measurement or grading sy tem the lipid treaks hould at least be clearly delineated from the others * In measuring the surface area of involvement in the aorta or coronary artery 40 per cent involvement with only lipid treaks may have an entirely different ignificance than a similar de gree of urface involvement with any combination of the other cla es of lesions

Vessels to Be Studied

The coronary arteries and aorta hould be examined in every instance *It is not fea ible to consecutively* tudy the cerebral vessels becau e in this country at least po t mortem permi sion for such examination is often not ob tained There are al o greater techni cal difficulties for making measurements of the degree of athero clerosis that would interfere with a reasonable ability to compare one tudy with another It m not ufficient to either examine the coronary arteries or the aorta alone The findings of the degree of athero sclerosis in a erie of aortas do not necessarily parallel tho e in the coro nary arterie Sex race age and geo graphic differences also affect compara bility of the degree of athero clero is in the aorta with the amount of athero clero is in the coronary arteries (ee Table 1) Therefore as a minimal ob jective in order to obtain a more mean ingful over all picture at lea t both ve sels should e tudied *Where routine* and con ecutive brain examination can e made and where ufficient attention can e given to the proper examination and grading of cerebral athero clero is it is of cour e highly de irable to do so

Any such study on cerebral athero clerosis however must take into ac count the fact that cerebral i chemia may develop as a result of athero clero is in carotid artery branches entirely ex ternal to the kull while the intracere bral vessels may show comparatively little change

The examination of other ves els in a piece meal fashion such as mesenteric arteries or renal arterie would not contribute any significant information to the over all picture At pre ent legal religiou and embalming ob tacles preclude the po sibility of routine ex amination on all the major vessel of the body

Preservation and Records

The conditions under which examina tion and grading of the vessel are con ducted will determine to a great extent the ob jectivity accuracy and compara bility of the findings Whether or not the specimens should be examined in a fre h or fixed state will depend upon the particular circumstances under which the tudy is being conducted Which ever the method it should be con i tently employed throughout the study because there is evidence to indicate that variations in grading particularly as regard coronary arterial luminal size exi t between the fixed and un fixed tate in the same pecimen Pro vi ion hould be made for preservation and empermanent torage of the ves el *A practical method* utilized by one member of this committee is excellent for this purpo e † Permanent torage of the ve el i not alway fea ible be cau e of expen e per onnel and time con uming effort involved In any event the findings hould always be reduced

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Stron J P McG ll H C Jr T jada C and H lman P L *Th N t al H tory* of Ath os l o C mparis n of th Early A rt l s o n N w Orl an Cu temala and Co ta Ri Am J Path 34 31–44 (July Aug) 19 .

† Holm R L. M G ll H C J Stron J P and Geer J C Techni s for Stud ing Athe sclerotic Le ons Lab In e t 7 1 –4 (Jan F b) 1958

Table 1—Relative Degree of Atherosclerosis in Aorta and Coronary Arteries in Consecutive Autopsies of Sudden Death (MF Cases) from Natural or Accidental Deaths

	Total Cases	A>C	A=C	A<C
Age group 30-50 years				
Females	46 (100%)	32 (12%)	28 (37%)	16 (21%)
Males	147 (100%)	11 (%)	49 (34%)	87 (59%)
Age group 51-70 years				
Females	72 (100%)	6 (36%)	28 (39%)	38 (53%)
Males	163 (100%)	35 (21%)	61 (37%)	69 (42%)

A>C Aorta has a relatively greater degree of atherosclerosis than coronary arteries
A=C Aorta has an equivalent degree of atherosclerosis to that of coronary arteries
A<C Aorta has a relatively lesser degree of atherosclerosis than the coronary arteries
(Spain H M and Bradess V Unpublished data from Wetchester Medical Examiner Coronary Study)

to some form of schematic diagram which can be permanently kept The elaboration and detail of such a diagram will vary with the needs and design of the particular study (Examples of simple and more detailed diagrams are listed in Appendixes B1 B2 and C)

Examination of the Vessels

The examination interpretation grading and measurement of the lesions in the vessels should be performed by competent pathologists well versed in the various lesions of atherosclerosis Preferably one examiner should carry out the entire study When this cannot be done a team of examiners should be trained in advance so that their measurements cross check with each other in order for the findings to be reasonably consistent and reproducible

Unbiased grading is difficult in the absence of a coding system Sometimes the situation demands that a specimen be examined immediately at the site of autopsy In such situations it is sometimes impossible to conceal age sex race and so forth But when possible the project should be so designed that the grading and examination can be determined in completely coded material

The method of grading lesions depends to some extent on the technic employed in dissecting the vessel The standard method of examining coronary arteries—cross sectional cuts or longitudinal dissections—are acceptable If the cross sectioning method is used these should be performed at intervals no further than 3 mm apart It is recognized that the WHO report suggests a 5 mm difference as being sufficient but it requires very little extra effort to reduce the interval and in the experience of some an interval as wide as 5 mm can miss a significantly large number of thrombi or occlusive atherosclerotic plaques In the longitudinal method the vessel is opened as far as possible with small coronary dissecting scissors The quantity and quality of the surface area involved is then recorded The three major coronary vessels must be examined

The aorta should be examined by a lengthwise opening and then spread flat The entire aorta should be described but for grading purposes the surface area between the upper margin of the first intercostal artery orifice and the bifurcation into the iliacs should be

considered . Some have recommended that the circumference of the aorta hould be measured at various levels This information would not appear to contribute to the olution of any of the desired objectives and would only add unnecessary detail to the examining procedure

Grading

It matters little as to what termin ology is used in the grading method provided the terms are clearly defined within an accurate and clear frame of reference If this procedure is followed regardless of the terminology employed the result of one study may then be reasonably compared with those of another The grading in the coronary arteries may take into consideration egments of steno i mean or maximum diminution in lumen size the extent of surface involvement and the types of lesions present If one excludes flat lipid streak there is considerable evi dence which indicates that the mean luminal diameter relates closely to the extent of urface area involvement In a study at the Albany Ho pital under the au pices of the Albany Medical School and the New York State Depart ment of Health it has been found that the curves for mean wall thickne s and mall lumen size parallel each other very clo ely Al o each measurement bore a imilar relationship to the inci dence of myocardial infarcts in both exes It i generally agreed that if either *the degree of urface area of* involvement of the oronary arteries or the maximum area of lumen reduction is u ed a a method of grading the end results hould be imilar There has been needl s concern over the number of individual who may have i olated egmental occlusive plaques in the coronary artery tree in the al ence of any ignificant degree of more wide pread athe ro clerotic involvement This occurs usually in young individual is uncommon and is often found in associa tion with an anomalous coronary arterial circulation or underlying inflam matory lesions of the ve sel wall The e occasional cases cannot materially in fluence the findings in any large scale autopsy studie Grading may be in terms of moderate or severe in terms of pluses or in percentage but these must always refer back to clearly defined limits or categories

In the recording sy tem the di tribu tion and extent of the different types of lesions hould be indicated wherever po ible As for the aorta the degree of urface area involvement should always be recorded with attention given to the distribution and relative propor tion of the variou types of lesions

Thrombi and Intimal Hemorrhages

There is a problem at times of differ entiating organized thrombi in the coronary arterie from athero clerotic plaque For recent thrombi this i relatively simple For remote and or ganized thrombi this i difficult and in many in tances not po ible Canaliza tion of the lesion was considered as po ible evidence in favor of an old organized thrombus as oppo ed to an athero clerotic plaque but this is by no means conclu ive However such errors that would ari e in the grading and cla sification of le ions relative to thi difficulty should not ignificantly influ ence the validity of the finding Mo t *evidence indicates that the more ex* treme and older coronary athero clerotic le ions are associated more frequently with uperimpo ed thrombi (ee Table 2)

The gross recognition and recording of intimal or intramural hemorrhage a a routine in any large scale autop y tudy can erve no meaningful purpo e and may lead to erroneous conclu ion Proper tudy of intimal hemorrhages re

Table 2—Frequency at Various Age Levels of Recent Thrombi in Sudden Death in White Males with Advanced Coronary Atherosclerosis (377 Autopsied Cases)

	Age in Years			
	Under 39	40-49	50-59	60-69
Number of cases with advanced coronary atherosclerosis (total)	46	116	126	89
Number of cases with recent superimposed thrombi	5 (11%)	26 (22%)	30 (24%)	26 (29%)

(Spain D M and Bradess V Unpublished data from Western Reserve Medical Examiner Coronary Study)

quires meticulous attention to detail with serial microscopic sectioning clearing techniques and so forth These procedures can generally not be performed with the minimal methodology available for large-scale studies This view is in no way meant to underestimate the desirability and potential significance of studying the problem of intimal hemorrhages This might very well be performed as a special investigation within a limited segment of an overall larger study

Other Techniques

Microscopic studies do not contribute enough additional information to significantly improve the exactness of the grading process to be required as a routine procedure Such techniques that determine elasticity viscosity of the vessel wall as well as detailed chemical contents of the lesions do not appear to enhance the accuracy of the grading procedure

The value of an index system of grading which arbitrarily assigns certain values to the quality of the lesions to the extent of the involvement etc is open to question Such index systems have been developed in comparing the degree of atherosclerosis in one population group of autopsies with that of another It was the conversion of this group that such an index system which arbitrarily assigns values to certain aspects of the lesions is biologically unsound and may lead to errors The state of our present knowledge of atherosclerosis does not as yet permit such quantitation

Injection techniques involving the introduction of radiopaque material into the coronary arteries or the utilization of plastic cast techniques are of considerable importance for studies designed to investigate the development of collateral circulation in the coronary arterial tree These techniques however are unnecessary and too detailed to be performed routinely in the studies under consideration The utilization of such techniques in order to gain information on the relationship between physical activity coronary atherosclerosis age and collateral circulation is important and should be encouraged

The Heart

In order to properly evaluate the significance of the atherosclerotic lesion in the aorta and coronary arteries it is essential that certain minimal findings in the heart be determined The condition of the valves and pericardium should be routinely recorded so that proper evaluation may be given to the factors that contribute to any increase

in the weight of the heart The heart hould be weighed with at the mo t only the ascending portion of the arch of the aorta attached It is not neces ary to determine or record right and left ventricular wall thickness ince uch errors as the inclusion of epicardial fat or papillary mu cle in the measure ment and the possibility of measuring tangential cuts a well as variations in wall thickne s at different levels would render compari on of re ults almo t meaningle s

The heart may be opened and ex amined in the u ually accepted manner whereby the cour e of the blood is fol lowed and the eptum is plit up from the apex to the base Pre ervation and proper examination of the coronary artery prevents a cros sectional slicing technic of the myocardium from being utilized

The pre ence of all recent infarcts should be recorded and hould include a tatement a to their ize location and age The clas ically recognized text book description of myocardial infarc tion furni he the criteria for recent infarct Any gro ly vi ible scar should be recorded In the ab ence of any other obvious cause for such a car and in the presence of advanced coronary athero clero i this may be regarded a a healed infarct Micro scopic confirmation of recent and old infarcts i de irable but not always e ential The condition of the coro nary o tia hould be noted

Information on Autopsy Record

All autopsy record hould include the age ex race and if pos ible to authenticate the country of birth country of residence duration of thi residence ethnic origin and occupa tional hi tory The immediate cau es of death as well a the ba ic or underlying di ea e proce or cause of death hould l e recorded Height and weight hould be determined and wherever fea ible the weight should be actually mea ured and not e timated If the weight is esti mated it should be so stated Panniculus thickness should be measured in the midline midway between the xiphoid and the umbilicus

Another method for increa ing the accuracy and completeness of ho pital records for the purpose of correlating certain finding with tho e at the autopsy is to send trained personnel into the home of the decea ed within everal weeks after the death and ob tain information from close relatives about moking exerci e diet and other living habit In the Albany tudy this has yielded significant information and has given more meaning to the pathological findings

Hypertension and Diabetes Mellitus

Autopsy verification of the previous existence of hypertension and/or dia betes mellitus would be highly de irable Unfortunately there are no certain morphologic findings for both condi tions—po itive or negative—to prove that the e did not exi t The pre ence of definite myocardial hypertrophy (predominantly of the left ventricle) the ab ence of any other cau e for thi hypertrophy in combination with arteri olar change particularly of the kidney is trongly suggestive evidence that hyperten ion was present at ome time during life The presence of intercapil lary glomerulo clero is is trong evi dence that diabetes mellitu was present

Standardized Post Mortem Examination as an Integral Part of Longitudinal Epidemiologic Studies*

A review of the variou project de igns of the epidemiologic studies a

*Dawber T R (Ed.) R port of the Co ference on Longitudi l Card ovascular Studies at th Hotel Beacon feld B ookl ne Mas. (June 14 18) 1957

described in the conference at Brookhaven in 1957 revealed that none of these studies had included any mechanism for the gathering of standardized autopsy material. This appears to be a serious deficiency. Any procedures whereby standardized post mortem data are collected on both sudden and hospital death of individuals on whom information has been obtained over many years in such studies can enhance the value of such investigation. It would seem *to be rather simple to arrange for the* pathologists in the involved community to set up minimal standards to obtain the necessary information relative to cardiovascular disease.

Unexpected Unexplained Sudden or Instantaneous Death

In the absence of adequate clinical laboratory or post mortem findings the use of unexplained sudden death as evi*dence of coronary* atherosclerosis with ischemic myocardial disease is at present generally not acceptable. The criteria *for the classification of cases* as those of sudden death varies considerably in different areas. Refinement of the definition of sudden deaths to include *only those cases in whom there has been* an eyewitness account and in whom the unexplained or unexpected sudden deaths have occurred within a matter of minutes is desirable. This group of cases should be clearly separated from those *in whom the* fatal event took a longer time and from those where the individuals were found dead with no witnesses available as to the exact *circumstances and their duration*.

In various parts of the world depending upon *the general health* and disease panorama of that area the proportion of cases *of sudden death that may be at*tributed *to ischemic myocardial disease may vary*. In this country it is highly possible that when the proper age sex and race factors are taken into consideration a considerable proportion of the cases of unexpected instantaneous death where eyewitnesses were available may be ascribed to cardiovascular disease. Before utilizing this category as evidence for ischemic myocardial disease in epidemiological studies more exact information should be obtained. A highly desirable project would be to set up a cooperative study among medical examiners offices for the purpose of determining the proportion of unexplained *instantaneous death* that are due to coronary atherosclerosis and ischemic myocardial disease. Such a study should be relatively simple to arrange.

Biostatistical Evaluation

It is recognized that the value of any morphologic study no matter how meticulous the method of grading depends for the stated purposes upon the ability to relate the autopsy findings to the population group from which the autopsies are obtained. Information must also be available concerning the characteristics of those individuals from this same population group who are not represented *in the autopsy series*. *Careful biostatistical evaluation* and design is therefore essential and should be part of every such study. The fact that previous statistical studies have pointed to dangers in drawing conclusions from hospital autopsy studies does not preclude the proper utilization of such material for the advancement of knowledge in this field.

It is the belief of this committee that with these minimal methods of studying autopsy populations a significant contribution toward a solution of the problems concerning the pathogenesis of atherosclerosis could be made. *There* is still no substitute in the understanding and solution of human disease for primary accurate observation in *the human laboratory itself*.

APPENDIX A

Definit on of Terms

(Fr m J P Stron_ from Proto ol of Latin American Project)

Fatty Streak Any intimal lesion that is stained distinctly by Sudan IV and that does not how any oth r type of chan e underlying

Fibrou Plaque Any firm elevated intimal le on wh ch in th fr h state is pal grey gli tening and tran luc t After staini g it may b partially or complet ly cover d by sudanoph l c d po its If a lesion con tain a y h morrha thromb is ul ra tion or calcificat n it will be cla ified under tho e cate ories and not as a fibrous plaqu

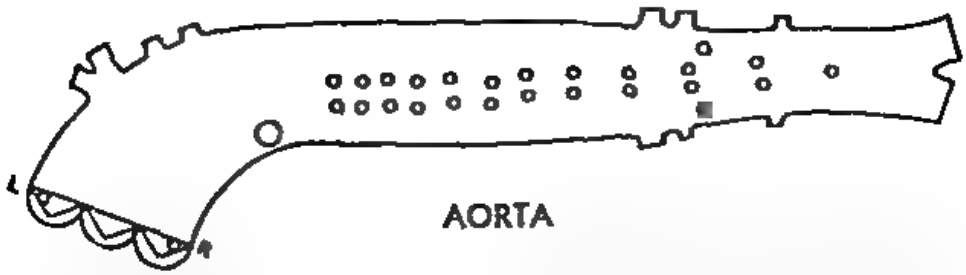
Complicated Le ion Tho e areas in wh h there i hemorrha e ulceration necro or overlyin_ thrombosis

Calcifi ation Areas in whi h there is calc um depo ition detectable eith r vi ually or by palpation without overlyin_ hemo rha_ ul rat on or thrombosi

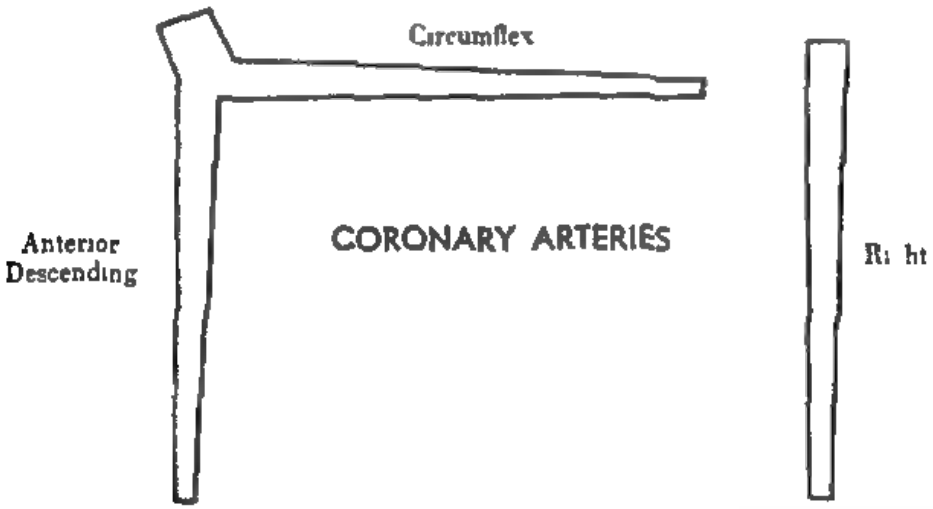
APPENDIX B 1

Preliminary Protocol of Latin American Project McGill H. C. and Strong J. P. et al

Necropsy No _____ Accession No _____



	Total Area Involved	Per cent of Involved Surface Composed of			
		Fatty Streaks	Fibrous Plaques	Hemorrhage Thrombosis Ulceration	Calcification
Descending Thoracic					
Abdominal					
Total					



	Total Area Involved	Per cent of Involved Surface Composed of			
		Fatty Streaks	Fibrous Plaques	Hemorrhage Thrombosis Ulceration	Calcification
Right					
Left Circumflex					
Left Anterior Descending					
Total					

APPENDIX B 2

Comparative Atherosclerosis Study

Laboratory _____ Accession No _____

Hospital _____ Necropsy No _____

Name _____

Age _____ yrs Sex M F Race _____ Occupation _____

Country of birth _____ x _____ yrs Country of residence at time of death _____ x _____ yrs

Principal Final Diagnoses

Primary disease _____

Immediate cause of death _____

Other diagnoses _____

State of Nutrition
- ( ) unknown
- ( ) severely obese
- ( ) moderately obese
- ( ) average or normal
- ( ) thin
- ( ) malnourished

Weight _____ lbs

Length _____ cms

Thickness of subcutaneous fat _____ cms
(midventral abdominal)

Code for principal diagnosis _____

Diseases possibly influencing atherosclerosis

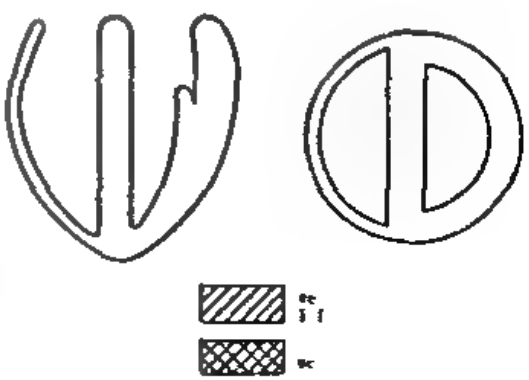
	+	−	?	
1	( )	( )	( )	hypertension established
2	( )	( )	( )	hypertension presumptive
3	( )	( )	( )	arteriolar nephrosclerosis benign
4	( )	( )	( )	arteriolar nephrosclerosis malignant
5	( )	( )	( )	pyelonephritis acute
6	( )	( )	( )	pyelonephritis chronic
7	( )	( )	( )	glomerulonephritis acute
8	( )	( )	( )	glomerulonephritis chronic
9	( )	( )	( )	chronic renal disease unclassified
10	( )	( )	( )	diabetes mellitus, established
11	( )	( )	( )	diabetes mellitus presumptive
12	( )	( )	( )	chronic alcoholism
13	( )	( )	( )	portal cirrhosis
14	( )	( )	( )	biliary cirrhosis
15	( )	( )	( )	rheumatic heart disease
16	( )	( )	( )	syphilitic heart disease
17	( )	( )	( )	hypothyroidism
18	( )	( )	( )	hyperthyroidism
19	( )	( )	( )	other endocrinopathies

Diseases presumably due to atherosclerosis

	+	−	?	
1	( )	( )	( )	angina pectoris
2	( )	( )	( )	coronary occlusion
3	( )	( )	( )	myocardial infarction
4	( )	( )	( )	cerebral thrombosis
5	( )	( )	( )	cerebral hemorrhage
6	( )	( )	( )	disabling peripheral ath rosclerosis
7	( )	( )	( )	mesenteric occlusion
8	( )	( )	( )	aortic occlusion
9	( )	( )	( )	aortic aneurysm
10	( )	( )	( )	arterial nephrosclerosis
11	( )	( )	( )	other unclassified

Heart

Weight _____ gms



APPENDIX C

From the Westchester County Medical Examiner Coronary Artery Study Spain D M
and Brade V A

M E No

Ethnic

Date
Height
Weight
Somatotype
Panniculus

Race

Case No Sex
Age

Immediate Cause of Death
Circumstances

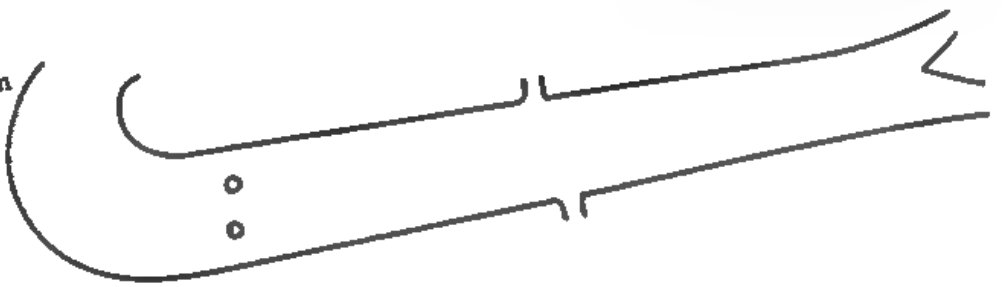
Basic Cause of Death

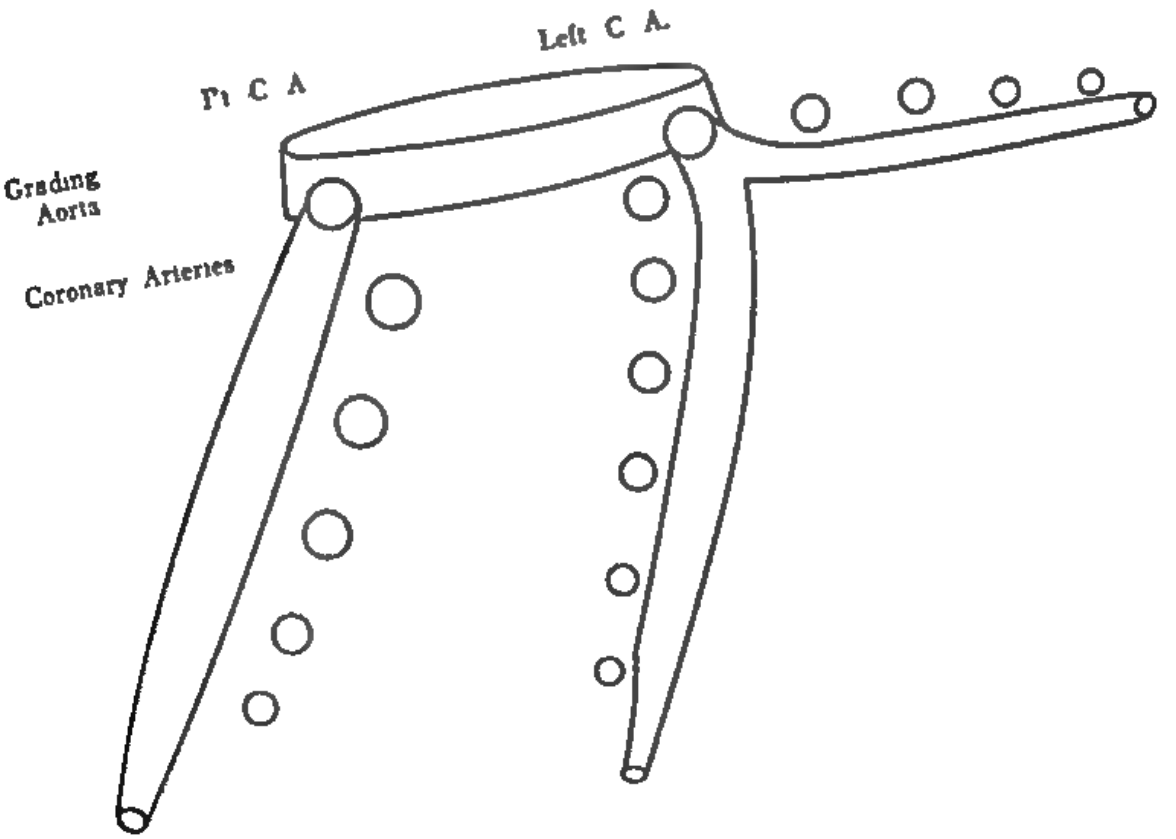
Occupational History

Fatty Streak
Plaque
Calcification
Thrombus

AORTA

Heart
Weight
Valves
Pericardium
Ostia
Infarcts
Location
Size
Age





COMMITTEE ON DIET, PHYSICAL ACTIVITY AND BIOCHEMICAL MEASUREMENTS

James Hundley M.D. Chairman

DIETARY intake and the expenditure of energy through physical activity are two components of the nutrition balance sheet of an individual or of a group of people. Methods of measuring dietary intake and energy expenditure are the subject of reports of two subcommittees.

Biochemical measurements are important in the analysis of dietary intake, in the analysis of the relationship of physical activity to cardiovascular diseases and in diagnostic studies in general. The uses and standardization of biochemical measurements are considered by a third subcommittee.

SUBCOMMITTEE ON METHODOLOGY FOR DIET APPRAISAL

Martha Truswell Sc.D. F.A.P.H.A. Chairman

Introduction

DIETARY surveys growing out of a suspected relationship between diet and and atherogenesis have increasingly become an integral part of the design of cardiovascular epidemiological studies. The Subcommittee on Methodology for Diet Appraisal was established to examine the existing procedures for collecting and processing food intake information to study the deficiencies in current procedures and to make recommendations for future research.

The methodology considered in this report is limited to the study of food consumption of individuals rather than for an average for groups of people. Thus problems of obtaining and processing information at the family or national level are not included. Discussions of computations and laboratory determinations will relate only to caloric values, protein content and fat content.

After a discussion and summary of the problems encountered in the collection and processing of individual food data, a second portion of the report will present several recommendations aimed at improving and clarifying the status of dietary surveys in relation to epidemiological studies.

Methods in Common Use in Dietary Surveys

There are several different dietary study methods in current use in epi-

demiological survey In order to yield meaningful information they mu t all include certain minimal facts about the subject such as age ex occupation height pre ent weight weight changes over a period of years activity health tatus (including inte tinal para itic in festation in subjects from certain areas) the usual number and time of daily meals and where the meals were eaten and current medication or dietary upplements

The evaluation of dietary intake in volves two procedures (1) the record ing of the foods eaten during the period of ob ervation and (2) the conversion of the intake record into units of food or nutrients

Collecting Food Information

There are everal technics in com mon u e for preparing a food record The outline below presents an arbitrary classification of thc e procedures in terms of characteristics which have im portant methodological implications The e characteristics are the time period covered the timing of the recording proce s and the method used to de termine amounts of foods In the e terms the method most commonly used or mo t rea onably considered for epidemiological studies are

(a) Intake at specific meals recorded con currently in terms of weights household mea ures or estimates of quant ty
(b) Intake at specific meals reported by re call in terms of e t mate of quantity or frequency of occurrence of food item
(c) Current usual intak reported either in term of estimates of quant ty of specifi food or by frequency of occurrence of food items
(d) Pa t changes in intake reported in terms of frequency of occurrence of food items

When there are concurrent record ings of intake at pecific meals (method (a) above) the conver ion of the intake record into unit of specific nutrients may be accomplished by chemical analysis of amples of the foods or by calculation from tables of food values When the observation involves recall (methods (b) (c) (d) inclu ive) nutrient values can be estimated only through the food value table

The concurrent dietary data can be recorded by the ubject by the person respon ible for the subject s food or by a trained ob erver Although the re call method utilizing either an inter viewer or a elf administered ques tion naire is one of the mo t convenient method of obtaining uch data it has its limitations For example whereas a diary or record will yield factual data an interview will yield only the ub jective average of an individual s re called food intake This is subject to a large human error factor—perhap the mo t important variable and certainly the most difficult to estimate

This error may be minimized by en li ting the subject s fullest cooperation and al o by the kill and talents of the interviewer The interviewer mu t be well trained in method of collecting and treating data He mu t be able to establi h rapport with the subject He mu t have knowledge of the cultural and socioeconomic factors operating in the community and peak the language or have a very competent inte rpreter He must develop technics of eliciting dietary information and of a embling this information If the subjects are to fill out questionnaires by themselve then the questionnaire mu t be pre tested under condition comparable to those of the survey area

The tress or apprehension cau ed by the survey it elf may bring al out a change in the subject s dietary prac tices He may temporarily alter his intake to conform to his conception of what he hould be eating If the subject is receiving public financial as istance he may report fewer or different foods than he normally eats becau e of fear that the stipend will be reduced In

other situations the ubject may eat better than he usually does to impress the workers

Arterio clerotic heart di ea e and hyperten ion develop over a period of year Ideally the entire past hi tory of nutritional and other environmental factor should be as essed The value of dietary tudie of individuals actual current intakes for hort periods—one day one week or one month—is que tionable unless it can be e tabli hed that the hort term tudies reflect usual eat ing patterns of the pa t

R w of L terat e

Studies of daily food intake have re vealed marked variations even in the same individual[1 3] Yudkin[4] using the daily records of postgraduate dietetic tudents at King Colle e de igned a tudy to provide data on the adequacy of dietary tudies taken for period of le than even days He found that caloric intake of an individual can differ by as much as 68 per cent from week to week hi data howed that the fat intake was largely respon ible for thi variation Thomp on[5] weighed the daily food intakes of a group of preg nant women and reported that the profile for the nutrient content of the individual diet appeared to retain its main characteri tics in two widely eparated weeks

Chappell[6] weighed her own food every day for more than a year She concluded that an ob ervation period longer than one week has little ad vantage over horter ones if only an average estimate of nutrients is de ired A more accurate estimate could be ob tained from three weekly record of weighing cho en easonally throughout the year McHenry[7] after studying the food intakes of a mall group of normal per on at interval throughout a year reported that the variation were of such magnitude that if the intakes for thi group had been recorded for a single week s period the results would have varied con iderably depending upon which week was u ed

Young and co workers[8] concluded that when daily diaries are used aver ages for groups did not appear to vary sufficiently from week to week to war rant more than a even day record In contra t to adequately study the intake of an individual it would appear that for some individual more than a single week s record would be desirable

Variations in the dietary intake de pend upon many factors especially food supply ea onal change and socio economic factors Religious and cul tural patterns alter intakes of certain food at pecific periods of the year The degree of internal variability and its relation hip to the design of the total tudy must be con idered in elect ing the time pan over which the dietary information will be collected

E timates of nutrient intakes calcu lated from the food table vary with the method of collection of information on food intake even when the same indi viduals and the ame food intakes are being studied Experience in compar ing nutrient values resulting from three different method of collecting data are ummarized by Young[9] as follows

1 *The d etary hi tory [defined by Burke as* the a era e food ntake over a con id rable period [10]] was compa ed with the 24-hour recall and the se en day record with 4-hour recall, as method of est mating the nutrient intake of an indi vidual and of a group Data for th e comp ons were obta ned f om three dif fer nt population gro p grade school chil fr n (New Yo k) hi h chool and col lege stud nts (Rhode I land) and pre nant women (Massachusetts)

2 For an ind vidual in any of the th ee popul t on g oups studied the 24-hour re call did not e th same estimate of dietary i take as th dietary history

3 For an i div du l in any of the th ee population group tudi d, the 24-hour re call d d not gi e the same estimat of d etary ntak as the even day r cord To descr be the intake of i d iduals th

two methods could not be used interchangeably

4 For the mean of a group the dietary history gave distinctively higher values for grade school children and for pregnant women than did the estimates obtained by a 24-hour recall. The history and 24-hour recall gave results which were in better agreement for the college group studied.

5 For the mean of a group the seven day record and the 24-hour recall tended to give approximately the same estimates for the dietary intake for most nutrients. This was true for all three population groups to which the two methods were applied: grade school, high school and college students and pregnant women. Under certain circumstances the 24-hour recall can be substituted for the seven day record in estimating group intakes.

Bransby[1] also reported that the values calculated from weighing household measurements and questioning of the children were in broad agreement for energy and nutrient content. These did not check closely with chemical analyses of the foods (Tables 1, 2).

Morrison[11] found that the memories of eight scientists for a 24 hour recall of food intake were extremely unre-

Table 1—Average Daily Energy and Nutrient Intakes Found by Four Methods of Survey in the National Children's Home, Harpenden (49 Children)

Item	Method of Survey: Weighing Value	Weighing SD*	Homely Measures Value	Homely Measures SD*	Questioning Value	Questioning SD*	Chemical Analysis Value	Chemical Analysis SD*
Calories	2660	507	2 71	423	2604	487	2 381	418
Protein gm†	[illegible]	18	89	16	81	18	89	16
Fat gm	96	22	107	21	95	19	81	14
CHO gm‡	366	69	363	52	354	[illegible]	394	69

* These are standard deviations for a single child and were calculated from the actual three day intakes of nutrients, the resulting values being divided by three to obtain the above figures.

† Protein—N x 6 0 as the diets contain both animal and cereal protein

‡ The starch values determined by the method adopted were increased by 21 per cent to permit comparison between analytical and calculated results.

Adapted from Bransby E R Daubney C G and King J Comparison of Results Obtained by Different Methods of Individual Dietary Survey Table 5 Brit J Nutrition 2 101 1948

Table 2—Correlation Coefficients Between Energy and Nutrient Values Found by Four Methods of Dietary Survey in the National Children's Home, Harpenden

Methods Correlated	Calories	Protein	Fat	Carbohydrate
W x H	0 94	0 90	0 93	0 93
W x Q	0 94	0 94	0 91	0 93
W x A	0 87	0 92	0.57	0 81
H x Q	0 91	0 87	0 87	0 91
H x A	0 85	0 82	0 53	0 71
Q x A	0 80	0 88	0 43	0 75

* W=Weighing Q=Questioning H=Homely measures A=Chemical analysis

Adapted from Bransby E R Daubney C G and King J Comparison of Results Obtained by Different Methods of Individual Dietary Survey Table 8 Brit. J Nutrition 2 103 1948

factory on an individual ba s How ever the averages for the group were similar to the calculated averages of the weighed food

There is a paucity of published data on methods of tudying long range eat ing pattern Trul on and McCann[1] in ve tigated the patterns of 39 Italian American male factory workers using a research hi tory method and repeated the study after a two year interval The mean intakes of the group for calories protein and fat as estimated from the two surveys did not differ significantly but there was considerable individual variation The correlation coefficients between the two urveys for the intake of protein fat and carbohydrate were approximately 0 5 The error in the method and changes in food supplies economic status occupation etc could have *contributed to these differences* The information collected may be a closer approximation of current eating practices than it is of long range pat tern

Marr[13] examined the dietary records of middle aged male British bank officers obtained by the weighing of food for two periods The second period was selected approximately ix months after the first period in an attempt to mea ure seasonal variations as well as reliability of reporting The data from 25 men are reported in Table 3 There appears to be considerable stability in the nutri tional habits of these men during this six month period For energy value and for the nutrients calculated (protein and fat) correlation coefficients for the two period ranged from 0 72 to 0 87 The co fficients for fat (land animal marine animal and vegetable) ranged from 0 81 to 0 87 (Table 3)

From the preceding di cussion it is evident that more knowledge is needed regarding the reliability of the results obtained by different methods in com mon use for collecting dietary informa tion It is not yet pos ible to utilize intake results obtained by one method for predicting results expected from *another method Further re earch* is needed on individual food consumption to identify the characteri tics of a diet pattern which are con tant and not greatly affected by daily and weekly variation

The problems encountered in the proc e sing of dietary data will be presented and discu ed in the next portion of this report

Table 3—Twenty f ve Ind idual Repeat Weeks Weighed Diet Survey

(Bank officers males 40-55 years inclusive)

	1957–1958 A erage Daily Consumption		
	First Survey	*Second Survey*	Correlation *Coeffic ent*
Calories (Cal)	2 169	2 819	0 81
Protein (gm)	89	83	0 7
Carbohydrate (gm)	3 6	338	0 89
Fat total (gm)	197	196	0 85
an mal (gm)	93	92	0 80
marine (gm)	6	7	0 81
veg table (gm)	98	27	0 87
Calories from fat (%)	41	40	0 83

Marr J W Heady J A and Morr s J N Pepeat Indi dual We ghe I Diet Surveys Proc Nutr tion S ciety 18 1 xi 1959

Table 4—Calculated Intakes of Food Components Comparison of Analysis of Duplicate Samples of Diets and Calculation of Their Contents

Nutrient	Method	Day 1	2	3	4	5	6	7
Energy (calories)	Analysis							
	Sample a		1,968	2,294	2512	2018	2051	2,384
	Sample b	1,521	1911	2,274	2553	2045	2,032	2411
	Difference		57	20	41	57	19	27
	Estimation	1,516	2152	2,260	2674	2,238	2,288	2,339
Protein (gm)	Analysis							
	Sample a	56.5	460	644	870	680	744	862
	Sample b	538	697	676	855	728	760	857
	Difference	27	63	32	15	48	16	05
	Estimation†	656	959	756	845	841	837	836

Heat of combustion

†Values derived from standard tables by multiplying total intakes of protein fat and carbohydrate by factors 5 65 9 45 and 4 1 respectively

Thomas R. U. et al. Nutritional Status of Children. XIII. Accuracy of Calculated Intakes of Food Components with Respect to Analytical Values. J. Am. Dietet. A. 26: 11 891 1950

Processing Dietary Data

There are three methods which the researcher may use to evaluate the dietary data (a) chemical analysis of representative samples of the food consumed (b) calculation of individual nutrients using food tables and (c) classification of information according to food usage. Each of these methods will be examined briefly.

Laboratory Analysis

Acceptable methods have been standardized for the analysis of food for a few nutrients. Procedures for pyridoxine determinations remain unsatisfactory. Analysis of food for total fat continues to present problems while the best method for analysis for specific fatty acids remains to be selected.

Work on these problems continues currently in the U. S. Department of Agriculture as well as in many other laboratories. A committee appointed by the Interdepartmental Committee on Nutrition for National Defense is working on further standardization of methods suitable for obtaining valid aliquots and for the analysis of food samples.

Table 4 shows differences in the analysis of duplicate samples as reported by Thomas.[14] Difficulties were described in obtaining consistent results from the analysis of duplicate samples from nonhomogeneous dishes such as meat stew. The greatest variation occurred when such foods as fried potatoes or green beans cooked with bacon fat were on the menu.

The best data on nutrient intake for a specific time segment are probably obtained by weighing and analyzing food items or aliquots of the diet as eaten. Expense and practicality may make such detailed observations infeasible. This technic has the further limitation that it can be used only for prospective studies which cover a specific time span and require concurrent observation. As with other methods the possibility exists that weighing and sampling may influence the kinds and amounts of food the subject eats by focusing his attention on his diet.

The main u efulnes of direct analy sis of foods in epidemiological tudies is for establi hing the reliability of re sults obtained from other methods

Calculat on from Food Tabl s

Dietary intake obtained by recall technics and meal recordings are fre quently converted to nutrient intake by use of the standard food tal les

There are a number of tudie in the literature which compare chemical analy is to calculated report Table 5 presents a ummary of the differences re ulting from treatment of the same dietary data by both laboratory analy is and calculation from food table [11-4] Caloric and protein values were within 10 per cent in more than half the cases but only 2o per cent of the fat de terminations were within this range Only 15 per cent of the calculated values for calories and protein varied from laboratory analysi figures by more than 20 per cent while more than 50 per cent of the fat determinations were out ide this range

Mo t of these differences can be at tributed to the calculation of the protein and fat content of the meat Tables of food composition prior to 1950 and ome of the more recent tables expres the values for raw meat on the ba is of carcass or whole-ale cut and have little or no information on trimmed retail cuts either raw or cooked It has been cu tomary to use the data for the raw meat in estimating nutritive values When meat is cooked there is con ider able lo s of fat into the drippings re ulting in a large reduction in calories and very little lo s in protein Fat adhering to the mu cle frequently i trimmed from the meat after it is cooked thereby reducing the calories further Therefore it i to be expected that the values for meat as calculated from the table will be high for fat and consequently for calories but will be within a rea onable range for pro tein If meat constitutes a large propor tion of the diet the calculated values for fat and calories for the diet a whole probably also will be too high

A recent publication[44] concerning the nutritive value of cooked meat helps to elucidate some of the apparent dis crepancies between analy and calcula tion of meat fat Future revision of food table are planned to provide more

Table 5—Comparison of Calculat ons from Food Tables w th Chem cal Analys s

Per cent Differ nce—Calculation vs Ch m cal Analysis

	−30 or Mor	− 0 to −?99	−10 to −199	±99	+10 to +199	+?0 to +?99	+30 or More	Total
C lories								
No of a es	0		29	218	73	28	??	378
?' of ca es	0	21	7?	577	193	74	58	1000
Fat								
No of cases	20	10	36	66	24	3o	68	259
of c es	77	38	139	255	9.3	13.5	?6.3	1000
Prot in								
No of cases	13	14		1?0	?9	14	8	318
?' of es	41	44	?21	535	91	44	24	1000

B sed n 29 tud es. Two of the tud es are Canadian f r are B tish and the rem nde are American *Th re are 23 d fferent studies report n= comparisons of cal ries, 25 of prote n a d ?1 of fat. These* tud es were publi he1 from 1937 t 19o) See eferences I 5 and 15 44

Table 6—Calculations of the Same Weighed Diets By Workers in Eight Different States—Based on 21 One-Day Diet Records

Means and Standard Deviations for Calories and Protein

	Mo	Wis	Iowa	Ill.	Mich	Minn	S D (a)	S D (b)
Calories								
Mean	1 918	1,820	1,872	1,893	1 875	1 936	1 894	1 904
S d *	432	329	387	351	417	390	406	398
Range	1,295	1 026	1 410	1,233	1 711	1,388	1,567	1 616
Protein (gm)								
Mean	65 6	61 9	57 2	709	61 9	55 9	67 4	57.2
S d.	17 2	15 9	15 4	33 1	15 5	15 3	15 9	16 9
Range	68 9	65 9	68 7	157 8	67.3	61 7	68 1	74 8

* Standard deviation

Unpublished data furnished by Dr Wilma Brewer based on a pilot study conducted by the NC 5 Tech Committee compilation of data by Harriet Roberts

detailed descriptions of cooked meat *Accuracy of calculations will depend* to a large extent on adequate description of a food item as it is actually eaten

It is recognized that direct chemical analysis is the best available method for determining the exact amounts of nutrients supplied by a particular food sample at a particular time However calculations using the best available tables of food composition when applied to a detailed food record compiled over a long period of time may *be more representative of usual intake* than chemical analysis of samples of foods eaten during a short period

In this connection reference is made to the background of the figures on nutritive value of foods published by the Department of Agriculture The values shown in these tables of food composition are not necessarily arithmetical averages of all analyses available for each nutrient in each food Many factors are taken into consideration in deriving the particular value shown such as variety seasonal and geographic differences production and consumption statistics shortage and manufacturing and preparation practices The nutrient values in the table *represent average values throughout the* year

The use of food tables for determining nutrient content of mixed dishes requires very special care since recipes will differ from day to day from household to household and from region to region Unpublished data from a pilot study[16] show wide variations in the calculation of nutrient content by eight different nutritionists using the same weighed diets and food tables (Table 6) The lack of adequate description of food *mixtures places an added burden on the* calculator's judgment in selecting the appropriate item in the food table

Calculation of the nutritive value of carefully obtained food records from appropriate food tables has many advantages The researcher has great latitude in selecting the specific components to be calculated The only limitation is the data in food tables With improvements in food tables the opportunities to search for possible interrelationships between different components of the food intake and other aspects of the subject's condition will be greatly extended

Food Usage

The third method of processing the dietary material is according to food usage Cla sification according to the frequency of use amount type of prepa ration periodic intervals of fea ting or fasting patterns of alcohol consumption and use of condiments may help de scribe the subject s nutritional environ ment A regional publication of the U S Department of Agriculture[46] describes homemakers meals (Table 7) Caloric and protein intake for the Birmingham and Minneapolis women were in clo e agreement However when the diets were classified according to food groups considerable differences were observed

No attempt has been made here to review the literature but results from this and similar reports suggest that further study and experimentation with the raw data in this ca e intake in terms of food items, may uggest im portant relation hips between food in take and cardiovascular disease

Discussion

A major defect in the collection and processing of dietary data lies in our inability to make precise or even ap proximate statements concerning the reliability of the various procedures in current usage Until such information is available it is difficult to evaluate the u efulness of dietary appraisal in epidemiological studies

Mechanical inaccuracies can be de creased through greater use of auto matic devices for the processing of data, while variations due to subjective judgments will be reduced to measur able proportions only through tand ardization of each procedure

For every dietary study con idera tion hould be given to establishing the degree of reliability for each tep in the

Table 7—One Day Food Intake of Homemakers

Average nutrient content

	Birm gham (261 Subjects)	M nneapol s (245 Subjects)
Calories	1,8 0	1 720
Prote n (gm)	57	61

Foo I intake accord ng to food groups
Per cent calories contributed by Ill f od gr ups

	B rm ngham (61 Subjects)	M nneapol s (245 Subjects)
	Per cent	Per cent
Milk cream ice cream and cheese	9 6	14.3
Fats oils	.33	10
Eggs	3 2	2.8
Meat poultry and fish	16 9	21 4
Dry beans pea and nuts	3 4	1.2
Potatoes and sweet potatoes	4 1	4 2
C tru fruit and tomato	1 6	2.8
Leafy green and yellow vegetables	1.5	1.6
Other vegetal les and fru ts	3 4	6 4
Sugars and oth r sweets	9 2	6 1
Gra n products	23 8	9 0

Adapted f om Clark F and Fincher L J Nutriti e Content of Hom maker s Meal F ur Cities Winter 1948 USDA Agricultural Information Bull No 112 (Mar) 1954 pp 3 and 30

collection and processing of dietary information. Such testing of the reproducibility of results should begin with a demonstration of the dependability of the instrument and procedures selected for obtaining and for processing the information. Equally important will be the reliability of the subject as an informant. He should be able to report repeatedly the same factual information. The interviewer must have the ability to interpret diet information objectively. For each procedure which depends upon a subjective interpretation, results from two or more workers should be compared. Through repeated interviews with the same subject and through the use of built-in cross-checks in a questionnaire, procedures can be pretested for a selected sample prior to the survey of the total population to be studied. Attention to the areas for which reliability is poor or for which reliability appears difficult to check will more clearly point out the deficiencies in presently employed methods.

In addition to the reliability that is the error variation in methods of collecting and processing dietary data, the validity of a method is an important criterion of its usefulness. The validity of the method will be judged by the extent to which the data it yield are a true measure of what the investigator wishes to describe. In other words, do the data obtained answer the question that is asked or satisfy the purpose of the investigator? The primary problem is to evaluate how accurately any method of collecting information measures dietary intake, keeping in mind that reliable data for a specific period such as a week or two may not be a valid measure of the characteristic diet of an individual.

Summary

The principles of dietary studies currently in use in epidemiological investigations of cardiovascular disease are described in the main body of the report.

There is need for dietary data on individual which can be related to other information about them. In planning dietary studies certain decisions must be made.

1. What are the objectives for the dietary study?
2. What hypothesis is under consideration?
3. What shall be the time span involved in the dietary study?
   (a) Intake for a specific time
   (b) Usual characteristic intake for some defined period
   (c) Combinations of these
4. What methods shall be used for collecting data?
   (a) Record
   (b) Recall
   (c) Composite of duplicate meals
5. How will amounts be reported?
   (a) Weighing
   (b) Measuring
   (c) Estimating
6. Who shall be the informant?
   (a) Subject himself
   (b) Person responsible for the subject's food
   (c) Both (a) and (b)
   (d) Observer
7. Who will record the information or sample and collect the food?
   (a) The informant
   (b) A trained interviewer
   (c) (1) A nutritionist or other professional person in food or nutrition or closely related field
   (2) Other persons knowledgeable about food
8. How certain is the investigator that his method is securing the information desired?
   (a) The schedule must be pretested unless it has been tested under similar conditions
   (b) Interviewers should undergo a thorough training period which includes actual collection and treatment of data in trial situation and information on the cultural and economic factors operating in the community
9. What additional information concerning the subject is needed?
   (a) Certain minimal basic facts about the subject must be known: age, sex, physical activity and data on physical measurements and present and

past health status that are to be studied in relation to the dietary data. Some social and economic data may also be useful.

10. How can the data be processed?
    (a) Chemical analysis of food composites or individual foods
    (b) Computation of energy value and nutrient from tables of food composition
    (c) Classification according to food usage patterns
11. What information can be obtained from the dietary intake?
    (a) The investigator may search for possible interrelationships between different components of the food intake and between the food intake and nutritional health or other aspects of the subject's condition
12. What are the gaps or lacks in methodology?
    (a) Lacks or limitations have been discussed in the main body of the paper and the following recommendations to help improve methodology for diet appraisal have been made by the committee.

Recommendations

The members of the committee recognize that ways must be developed to minimize current problems noted in the present methodology of securing information on food consumption of individuals for use in epidemiological studies of cardiovascular disease. They make the following recommendation.

A *Assembling of Published and Unpublished Work Relating to Methodology of Diet Appraisal*

The committee recommend *that a* collection compilation and critical evaluation be made of published and unpublished work relating to methodology for diet appraisal particularly material on validation and reliability of methods currently being used. It is recommended that such an evaluation be published and be made available to workers in the field of epidemiological studies of cardiovascular disease.

B *Preservation of the Original Dietary Data*

The committee suggests that a means of preservation of dietary data be explored. Government agencies can use the facilities of *the* National Archive. For other arrangements through appropriate journals with a repository such as the Library of Congress will *allow for storage and later use. With* such a system well collected dietary material from numerous earlier studies, reported only in terms of carbohydrate *protein and calories for example could* now be processed for other nutrients.

C *Continued Study and Development of Methods of Chemical Analysis Food Composition Tables and Classification and Patterns of Food Usage*

(1) Chemical Analysis—The committee recommends continued research on the chemical analysis of food and the standardization of methods. Analysis for fat, techniques of collecting and computing food, methods of analysis of such composites as well as better analytical methods for nutrients such as fatty acids and pyridoxine may be cited as areas for investigation.

(2) Food Tables—The committee recommends the expansion of the tables of food composition currently available. Activities are under way to improve and extend several of these. However more information is needed concerning composition of recipe dishes or mixed *dishes regional dishes and commercially* prepared or partly prepared ready to eat food or food mixes.

One possibility for covering regional variations in nutrient composition of locally grown and locally consumed foods would be to have the U. S. Department of Agriculture collect, compile and publish such information when available.

(3) Classification of Food—It may

be as important to investigate the intake of certain foods types of food or groups of food as it is to estimate the consumption of nutrients they supply The committee recommends that additional study be devoted to this area particularly to accommodate the testing of current hypotheses in epidemiological studies of cardiovascular disease

D *Processing of Dietary Data*

To standardize and expedite the processing of dietary data the use of machine computation should be further explored

The committee recommends that more systematic effort be devoted to utilizing modern machine devices to calculate dietary intake information into nutrients food groups meal patterns etc This has already been done for a few studies but there is no standardized procedure The saving of time and money as well as the increase in accuracy make this most important

E *Research in Methodology*

(1) Short Method for Obtaining Dietary Information

The committee recognizes that there is need for new approaches to methods for obtaining dietary data that can be used in epidemiological studies Since the objective of epidemiological studies is to search for evidence of possible association between a dependent variable (such as ischemic heart disease) and an independent variable such a study usually is concerned with a relatively large number of persons who are to be classified into subgroups which will differentiate the persons according to the independent variable When food intake is the independent variable to be examined there are major difficulties to be overcome because unlike such variables as age hours of sleep or even number of cigarettes smoked per day food intake is a multifactor variable which can be classified in many different ways In any study in which diet or level of consumption of pecific commodities or nutrients is to be one of the independent variables one or more methods of classification must be decided upon and then the data collected in such a way that this classification will be practicable

If an hypothesis about the relation of a specific nutrient food or group of food to a disease is to be tested this will determine the axis on which persons will be classified In many recent studies of ischemic heart disease association of the disease with amount and types of fat and with the percentages of total calories obtained from such sources have been of principal interest The results of such studies in the United States have not proved definite associations Consequently there is a desire to take a new look at the total problem of food intake dietary patterns eating habits etc and to correlate this with calorie balance If this is carried out with no hypothesis to guide the collection of data what steps can be taken to develop procedures for searching for evidence on which to base some hypothesis for more intensive and controlled investigation?

Essentially the problem is to find and describe the major differences among individuals with respect to foods eaten and to develop practical methods for obtaining information needed for classifying people according to selected dietary characteristic If groups can be clearly differentiated by use or non use *high or low use of any food item* or items or other dietary characteristics then such characteristics can be tested for association with the disease

It is proposed therefore that a short, simple schedule for collecting information about types of foods used and meal patterns be prepared and used for questioning persons in several samples of selected populations The populations studied should be from communities

known to differ with respect to mortality or prevalence rates for ischemic heart disease. These also might be groups with different rates within a community. The objective would be to compare either mortality or prevalence rates for persons in various diet classifications.

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44 Le t R M d Od D H V Th N t
N t f Cook d M t Okl h m S e L l
ty Ag l p S M H P bl (M P 49)
(M) 1 8
4 W t B k d M H A L C mp t f
F l—R P w d P p d U S D p f
Ag l Ag l l H dbook N S W h
H D C 1940
4 Cl l F l F h L J N C t
f H m m k M l H Cl W 1948
H m F m Rese h B H Ag lt l R
h S rv U S D p f Agr lt Ag l l
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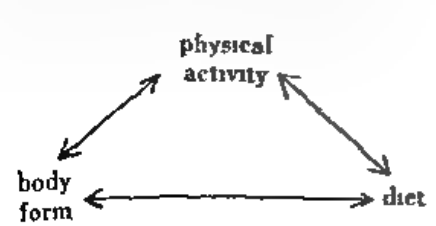
SUBCOMMITTEE ON METHODS FOR ACQUIRING INFORMATION ON PHYSICAL ACTIVITY AND BODY FORM

Harwood S Belding Ph D Chairman

1 The Task

SUFFICIENT suggestive evidence has been collected of relationship between level of physical activity and development of cardiovascular disease to encourage a rash of hypotheses regarding the mechanisms involved Meanwhile further epidemiological studies are required better to define the relationship Such studies will continue to be complicated by interactions of physical activity with body form (constitution) and with diet It is obvious that any one of these factors may influence the other two The fact that the subject of dietary measurements is handled by another subcommittee should not be taken as indication that relationships of any one of these factors can be understood without attention to the other two



The task of this subcommittee is to consider means by which the physical activity and body form of population groups or of individuals within such groups may be assessed The consideration of hypotheses and the evaluation of evidence *now available* is *beyond the* scope of our assignment We deal here only with methods of assessment of physical activity and body form

Our approach to this problem was first to decide what it is that we should know about physical activity of a population under study then to indicate and discuss means for acquiring the information This approach was repeated in dealing with body form

2 *Physical Activity*

We are agreed that whether the purpose be to describe two homogeneous population groups having different activity habits or to describe individuals in a population under study it is necessary to know (a) what the physical activities have been and the environ

mental conditions under which they have been conducted (i e what have been the stresses) and (b) what physiological demands the activities have made (i e what have been the strains)

A *Description of Physical Activities (The Stresses)*

(1) Average Daily Energy Expenditure

This is essential information for even the most primitive classification into activity groups namely relatively active and relatively sedentary It will also *be most closely related to studies of effects of* nutritional factors Such information based on activity level in the immediate past of subjects will probably be adequate for epidemiologic purposes Ideally information will be sought over the lifetime and at the least it will be needed for the adult years

Exactness of estimate of average daily energy expenditure cannot be expected from technics applicable to epidemiological studies of *long term physiological* changes It seems likely that the general level of physical activity can only be described in terms of about three grades light moderate and heavy* For uniformity in usage of *these terms* we suggest that light be used to describe daily activities involving up to 2 400 calories of energy expenditure per day for a man of average† size moderate be used for 2 400 3 200 calories and heavy be used for expenditures in excess of 3 200 calories Since the energy requirement for rest is about 1 800 calories/day light represents up to 600 calories of work moderate up to 1 200 *and heavy above 1 200* · Assessment may be by interview or more accurately by study of the characteristics of the job performed and supplementary information from available sources on activities during off job hours Of use in these connections are summaries that have been published on the energy cost of various tasks (see Passmore R and Durnin J V G A Physiol Rev 35 801 840 (Oct) 1955) However some *common tasks have not been studied* Furthermore published values may be

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It is believed that classifying workers with reasonable accuracy into three categories of physical activity requires visits to the job site by experienced observers and under ideal circumstance measurement *of the energy* requirement of any tasks with which the observer is unfamiliar It should be recognized that when such classification rests primarily on occupation the assumption is made that leisure time activities contributed that the energy expenditure of the sedentary *group* in reasonably enough to compromise the difference *in energy* levels between the sedentary and moderately active groups It may be noted that this was actually the case in the study of miners and clerks at Fife Scotland in 1959 where it was found that in 19 coalmines the energy expenditures in activities not at work was 1 490 calories per man per day while among 10 clerks it was 1 410 calories Common sense classifications will place clerks in *the light activity* group and miners in the group which requires heavy physical activity but the total energy expenditure of miners was 3,660 calories and that of clerks 2,800 The difference in total energy expenditure of 860 calories is not easily large and means that for purposes to define a group employed in moderate physical activity one is attempting to distinguish differences of the order of only 300 or 400 calories. To do this with precision obviously requires a good deal more than just a visual questioning

When the observer does not have firsthand knowledge of actual job conditions it is believed that a satisfactory classification *of the* activity level can be made by using two classes designated sedentary and physically active with a third group designated as moderately active and/or uncertain This kind of classification was used by Morris J N Heady J A Raffle P A B Roberts C G and Parks J W Lancet 1953 1053 1057 (No 21) 1953 in classifying death certificate data in activity groups based on last known occupation by workers in the Minnesota Laboratory of Physiological Hygiene study of railroad employees.

† A man of average size one who weighs 65 kilograms 68 cm tall and has a surface area of 1.85 m For most purposes body weight is an adequate measure of resting energy expenditure Its accuracy as a measure of average daily energy expenditure varies somewhat with the amount and kind of work done The arbitrary calorie levels for grades of work may be adjusted downward or upward in accordance with percentage deviation of an individual's *weight from 70 kilograms the* degree of accuracy required and the range of work energy being studied may indicate the use of more nearly precise formulae

mi leading because the energy expendi tures for a particular job may not be equivalent from country to country due to differences in methods For example E H Christensen s values (Symposium on Fatigue Floyd W F and Welford A T (Ed) London H K Lewis 1953 pp 93 108) for various jobs in the Swedish steel indu try do not cor respond to those of Ford A B Heller stein H K and Turrell D J (Cir culation 20 537 548 (Oct) 1959) for these jobs in Cleveland

For relatively homogeneous popula tion groups with establi hed and con sistent patterns of activity (e g pri on populations or fishermen in a fleet) it would be worth while to make sample measurements of oxygen utilization and to maintain an accurate log of time spent in various activities as a means of improving the estimate of total energy utilization A little arithmetic will show that the large t errors in estimat ing work calories are in the e timation of time spent at any particular task Probably the most accurate index of total ener gy expenditure (for such popu lations) may be acquired by careful assessment of the calorie value of the diet

Meticulous application of existing method for estimating over all daily energy expenditure cannot be expected to have accuracy better than ± 300 calories This degree of accuracy will not be required for most epidemiologic studies

(2) Variety and Pattern of Act vity

This information may be as important as that on average level of activity Relatively brief but frequent bursts of activity may be significant for estab lishing or maintaining mu cular power and cardiovascular capacity among those classified as less active on the basis of average daily energy expenditure Furthermore man being rhythmic as re gards activity level the very rhythmic pattern between work and rest may affect his long term well being

Desirable knowledge includes cus tomary peaks of energy expenditure and their frequency The types of mu cular activity al o may be pertinent e g whether static or dynamic (becau e static heavy effort affects cardiac filling —the Valsalva effect) whether heavy or light whether involving few or many mu cle groups (ee Lehmann G Prak ti che Arbeit physiologie Stuttgart Ceorg Thieme Verlag 1953) Informa tion on activity during and out ide of gainful employment including exual activity and leep habit is needed for a reasonably complete picture

Methods involved in as e ment of activity peaks and pattern of activity are generally similar to tho e utilized for determining the total daily energy ex penditure The emphasis here is on determination of the history of heavy demands on the circulation and on dis tinguishing between situations involv ing free filling and re tricted filling of the heart The likelihood of bias in the subject s evaluation of his maximum efforts is not known Error of e timate is encouraged by the fact that most ac tivities (whether they be brick laying climbing hill or playing tennis) may be accompli hed at widely varying speed

Data on current on and off jol activi ties of subjects can often l e quite ac curate However uch will not be re garded as sufficient for purposes of studies of on et of chronic disea e Collection of data on the lifetime of prior activity by interview of subject relatives and associates is necessary despite the fact that such data will be le s accurate

In taking a detailed activity history one mu t inquire carefully regarding the principal energy consuming tasks on the job and the time spent doing each one (See Appendix 2 for check list of items to be cove ed in ques-

tionnaires regarding phy ical activity) Attention hould al o be paid to rest pau es and activities requiring little or no energy the mode of transportation to and from work and the activities during recreational periods Ouestion hould be directed at the amount of time spent walking both on the job and off the job Care should be taken to see that the subject does not confu e standin$_{g}$ with walking In all c ses an attempt hould be made to obtain some estimate of the time spent in each task

Each subject should be asked to de cribe the most trenuous ta k which he performs and the frequency with which he performs it It is believed that this question should be left to the end of the interview since it is a lead ing que tion which sometimes leads to overstatement and boasting Under ideal circumstances then an interview would yield an estimate of the total energy expenditure in three grades plus an indication of the intensity and fre quency of the significant peak loads

Again under good circumstances pecial que tioning into leisure time ac tivities should be carried out Experi ence has shown that the majority of energy consuming leisure time activities are of the type which demand a low rate of energy expenditure and center around gardening home repair and hobbies requiring tools or ports such as golf (except on hilly courses) which do not require peaks of high energy expenditure However there is a group of men who spend time in gyms participating in bona fide high peak energy expenditure ta ks uch as squash and handball requiring the utilization of a $_{g}$ood deal of anaerobic energy Anaerobic exerci e of this kind is quantitatively and qualitatively different from the u ual phy ical activity of the average wage earner with or without hobbies and in those situations where it is fea ible men of this type hould be placed in a eparate category It is believed that these men are easily identi fied if the observer will take time to make a di tinction between men who go to the gym for companionship and only a token amount of exercise and those men who spend three to four hours a week in participation in high energy level conte ts

It should be empha ized that there has been practically no systematic effort to validate an activity history When one actually examines the available data it is found that very little is actually known regarding physical activity pat terns and energy expenditures of the American wage earner living in large urban centers

Since walking is an activity which requires more energy expenditure than that found for many production workers in indu try (Hellerstein H K and Ford A B J A M A 164 225 231 (May 18) 1957 Ford and Hellerstein Cir culation 18 823 832 (Nov) 1958) the time pent in walking by sale men and office workers in large banks and indus trial concerns is of real consequence Very little is known concerning walking patterns of such men whose work would be cla ed superficially as light, but which may actually fall into a higher category

The time di tribution of activities is important but it may be just as im portant to identify the man who always walks rapidly and prefers walking up stairs to ridin$_{g}$ an elevator It should be noted that increasing the peed of walking on the level from 2 0 to 4 0 miles per hour increases the calories ex pended per minute (but not per mile) for a man who weighs 160 pounds from 3 2 to 5 8 In this context it may be noted that there is no information on the distribution of walking peeds among American men Walking peed might be u ed as an index of drive in tudies where this was a parameter of interest

Pulse rate* and pulmonary ventilation† are correlated with the energy demands of activity. If a high degree of correlation were established for such physiologic responses, data obtained from 24 hour use of monitoring apparatus could be converted to values for *peak and daily energy expenditure*.

See Appendix 1 for sources of information on methods for objective measurement of energy utilization.

(3) Environmental Factors

Certain components of the environment may enlarge or diminish the stress of activity. Of most obvious importance is the thermal environment. Work in heat is accomplished at greater cardiac cost (e.g., Robinson, S., Turrell, E. S., and Gerking, S. D., Am. J. Physiol., 143: 21-31 (Jan.), 1945; Pelding, H. S., and Hatch, T. F., Heating, Piping and Air Conditioning, ASHAE Journal Section, 127: pp. 129-136 (Aug.), 1955) and with distribution of a substantial fraction of output through cutaneous vessels; habituation to cold involves different utilization of the cardiovascular system. The general thermal environment should be a matter of record, particularly if comparisons are to be made between population groups from geographical areas with widely different climatic conditions. For subjects exposed to processes hot in performance of their jobs, the fact of exposure should be recorded.

Objective data on physiologic responses to work (vide infra) should be collected under standardized thermal conditions; if this is not feasible, the environmental conditions should be described.

Other environmental factors of possible *consequence and interest include* barometric pressure, noise and vibration.

The sociologic and cultural environments in which life activities are conducted may be of importance in potentiating or canceling effects of physical activity per se. It is hardly within our sphere of competence or responsibility to point out methods of describing the environments in terms of the tresses (tensions or drives) which they present. Nevertheless, we recognize that some jobs involve threat of catastrophic consequence for mistakes in judgment or performance (e.g., piloting a plane or other public transportation, high level decision making) and that individual workers on such jobs may or may not *be affected by these stresses, depending* on temperament, but the presence of such stress should be a matter of record in epidemiologic studies. In other instances personal drive may result from competition. This may be reflected in average daily energy expenditure (pace of physical activity), but if the "drive" is nervous rather than physical in its expression it may not be measurable by available methods.

B *Description of Physiologic Strains of Activity*

(1) Occupational Activity

Descriptions of the work pattern and environmental conditions of a study population are no more important than *knowledge of the physiologic responses* of the population to the stresses of life activities. Significant lead toward identifying causes of cardiovascular (CV) disease may be found in compari-

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Christensen (loc. cit.) classifies the heaviness of work as follows:

	Cal/hr	Pulse/min
unduly heavy	750	above 175
very heavy	600	150-175
heavy	450	125-150
moderately heavy	300	100-125
light	150	75-100

These values apply for the work itself. They *do not* include rest pauses.

† Developers of the IMP (see Appendix 1) believe that respiratory minute volume is closely proportional to energy expenditure over a wide range of activities. The IMP yield direct information on respiratory minute volume.

sons between populations having apparently similar activity levels but exhibiting different degrees or types of physiologic responses Heart rate blood pressures blood volume and composition cardiac output and respiratory responses to customary activities represent only a few of the parameters potentially important in relating work to CV disease

The work physiologist relies on work and recovery pulse rates as important indicators of overall CV strain produced by activity A lower pulse rate is held to be consistent with less CV *strain and greater cardiovascular fitness* Cardiologists rightly point out types of CV abnormality in which such interpretations may be erroneous Actually we cannot recommend sole reliance on pulse rate or any other single parameter as a measure of CV strain

Burgher has again pointed out (Burgher G C E and Marten G A Proc XII Internat Cong Occup Health 3 113 118 1957) the desirability of using pulse pressure during activity in conjunction with pulse rate and has demonstrated how such value may be utilized to derive an index of heart work

(2) Standard Activity

In comparing populations having different activity levels it will often be useful to know their responses to a standardized level and kind of activity Presumably such activity would be selected to lie within the *competence* of most members of the population under study Walking on the level or up a moderate grade is probably the best activity for these purposes *The most meaningful* physiologic values will be obtained after subjects have been *exercising* for *some* time and have acquired such a steady state Recovery pulses blood pressures etc will also have some meaning (cf Johnson R E Brouha L and Consolazio F Rev Canad Biol 1 491 503 (June) 1942) The Masters stepping exercise might be modified for this purpose but probably will not be suitable at standard pace because it represents heavy work (classification of Christensen loc cit based on data of Ford A B and Hellerstein H K JAMA 161 1868 1871 (Aug 24) 1957) in which a steady state will ordinarily not be achieved by most subjects

(3) Maximum Activity

Knowledge of the maximum capacities and limitations of the CV system would be useful in comparing populations and especially in studies of the time course of change in capacity among groups with different activity patterns Such information could also provide an objective check against acceptance of subjects exaggerated claims of physical prowess

The problem of estimating maximum capacity for work for middle aged and older subjects is difficult because we will not accept risk of injury and to require maximum effort may or may not involve such risk The need for a means of determining capacity without requiring maximum effort While there is no established reliable means for accomplishing this leads have been provided Astrand (Thesis from Gymnastika Centralinstitute Stockholm 1952) in his study of working capacity of normal subjects in relation to age showed that heart rate at submaximal work levels can be used to predict maximal levels of work output with fair accuracy His subsequent research has been designed to evaluate this concept for less fit and older populations (results not yet available)

German (Muller E A Freiburger Symposium Heidelberg Springer Verlag 1958) and Dutch workers have been predicting maximum level of sustained work by measuring pulse response to increments of work on the

bicycle ergometer * The exercise may be terminated at a level predetermined as safe (e g 125 or 150 beats per minute), or on the basis of ECG changes The curve of heart rate against work is then extrapolated to 180 beats per minute (or a lower value for an older subject inferred from Robinson S Arbeitphysiologie 10 251 1938) The validity of such predictions depends on the degree of extrapolation that is required We would endorse support of studies further to develop and define the accuracy and sensitivity of predictions of work capacity based on heart rate and/or respiratory ventilation

The extra circulatory burden of exposure to warm environmental conditions during a performance test may be considerable (vide supra) For example our computations using Robinson's data (loc cit 1945) indicate extra demands of 1 5 liters per minute or more for cutaneous circulation when men are resting in heat and up to 3 0 liters or more when they are working It is clear that thermal stress must be minimized or controlled in application of tests such as those described above Research may be warranted to determine the usefulness of responses to thermal stress (in lieu of exercise) as a measure of cardiovascular status and capacity

C *General Observations*

(1) Prospective vs Retrospective Studies

The working group spent some time in weighing the opportunities for gathering information on physical activity in relation to development of CV disease (1) when the population is chosen for a longitudinal study in advance of major CV incident and (2) when the population is chosen afterward The cost of the two types of approach is not our direct concern but since the prospective type of study costs much more the results of our deliberation on this subject may be of interest

It seems to us that the possibility of collecting accurate data regarding level and type of physical activity is much greater while the subject is well The present average and peak levels of activity and the physiological responses to work are directly observable After sickness is recognized these advantages of direct observation are lost and the prospect of obtaining an unbiased accounting of prior total physical activity from the subject or observers is lessened because of the vagaries of memory To the extent that there is a long term employment record on members of the study population this disadvantage will of course be less important

(2) Two Approaches in Study of Physical Activity

The information needed and the methods in attempting to find relationship between physical activity and CV disease will vary with the type of approach that is intended We recognize two major approaches study of two or more population groups assumed to differ in physical activity and study of a single population supposedly with diverse activity levels and attempting to classify its individuals as to physical activity

(3) Study of Populations Selected by Occupation

When the study is of the first type the energy demands and type of work should be ascertained by direct observation by a work physiologist using techniques for sampling oxygen consumption of special activities and time study as required with view to ascertaining average total energy requirement and peak energy requirement and distribution of deviations from average Such

* See also Correlation of Static and Physical Endurance USAF IA A Test of Physical Performance Based on the Cardiovascular and Respiratory Response to Gradually Increased Work Bruno Balke USAF School of Aviation Medicine Randolph Field Tex Project No 21-32-004 Rep No 1 1952

data are necessary to show how differ ent the two populations really are Sufficient data on employment history must be examined to a ure that em ployment has been (or in prospective tudies will continue to be) stable

A representative sample of each popu lation should be chosen (minimum re quirement) for admini tration of an interview designed to establi h average and deviations from average total daily activity as well as maximum activity levels over the adult years The same sample should be subjected to body measurement so that homogeneity or differences in build may be establi hed for groups that are to be compared (vide infra)

It would be desirable to have total activity and body build data on the total population as a ba is for sorting out subjects who are atypical It is al o desirable to have information on current cardiovascular status of the sample or the full population whether available exercise tests can di fine cardio vascular tatus ufficiently for purposes of epidemiologic studies is not known but we con ider the likelihood promis ing

(4) St dy of N hom g eous Pop latio s

When the study is of the second type of a population which is apparently nonhomogeneou as regards activity level and type it becomes necessary to cla sify each individual on the basis of physical activity This should be ac compli hed by interview of all members of the group In addition it would be desirable to te t the validity of inter view data by admini tration of the same interview to a sociates at work and to friend as well as by examination of employment records

Categories of work that may be differ entiated are light moderate and heavy as regards average phy ical activity Peak level may be classified as high moderate or low For tho e having moderate to high level peak activities it may be useful to differentiate primary requirements of peed (intermittent muscular contraction) endurance (for extended periods) and strength (lifting pushing carrying and so forth)

Minimum acceptable mea urements of body form will be needed on all mem bers of the population

Comments made above regarding de sirability of measures of CV function and capacity through exercise tests are equally applicable in this type of epi demiologic study

(5) Retro p ct ve St d es

Some parts of these observations have been applicable only to prospective studies It is recognized that direct measurements will have reduced useful ness in studies of factors related to onset of CV di ease using populations in which heart disease is already pre ent When the interest in m progress of CV disease after its fir t manifestation ome of the direct measures will still be ap plicable

3 Body Form*

A *Information to Be Sought*

Body form may be related to the oc currence of cardiovascular disease (a) directly through some un uspected or uncontrollable mechani m (genetic link age) or (b) indirectly via ome other factor(s) now thought to be a. ociated with cardiovascular di ease such as oc cupation biochemical tatus phy ical activity or diet

Even if the primary association of body form with cardiovascular disea e is stronger than its a ociation with other atherog nic or hyperten ogenic factors the causality is obvious ly not direct that i body form does not in

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The W ki g Group expresses its apprecia tion to H T E Hertzberg W W H wells and W M Krogman for suggest ons wh ch ap pe r in this section

itself cause di ea e As in all epi demiologic tudies the underlying mecham m will till have to be sought in the laboratory

(1) R lat on to Card ovascular D sease

Other committees be ide this one—pecifically those on pathology and genetics—have cited the evidence for an a. ociation between body form and coronary heart di ea e Such evidence comes from two ets of investigators u ing the omatotype technic for de cribing body build Gertler M M and White P D (Coronary Heart Disea e in Young Adult Harvard Uni versity Press 1954) working with clini cal material characterized young cor onary patients as predominantly meso morphic (bony muscular) and econd arily endomorphic (round fat) Spain D M Brade s V A and Huss G (Ann Int Med 38 254 277 (Feb) 1953) on autopsy material called such *patients predominantly mesomorphic In* a later tudy Spain D M Bradess V A and Greenblatt I J (Am J M Sc 229 294 301 (Mar) 1955) re ported that among endomorphs and mesomorphs but not ectomorphs (linear a thenic) coronary clerosis paralleled erum beta lipoprotein levels The consi tent results of these two ets of investigators require confirmation with additional measures of body form and with better controls For example 27 of Gertler and White s 100 coronary patients but very few of their un matched controls were Jewish

Many reports too numerous to cite relate hypertension to stocky rather than lean builds Hippocrates was merely the first to note the apoplectic habitus Malignant hypertension has however been said (Perera G A and Damon A Arch Int Med 100 263 265 (Aug) 1957) to occur in women ignificantly leaner by the height/cube root of weight index than women of the same age from the same clinic with either benign hypertension or no known di ea e

The tocky mu cular phy ique re portedly prone to both types of cardio va cular disea e coronary heart di ea e and hypertension thus contra t harply with the lean phy ique found more us ceptible to tuberculo is in recent large cale pro pective tudies both in England and the United States (Berry W T C and Nash F A Tubercle 36 164 171 (June) 1955 Palmer A L Jablon S and Edward P Q Am Rev Tuberc Pulm Di 76 517 539 (Oct) 1957) So once more Hippocrates may have been right in contra ting the plthi ic and apoplectic habitu

(2) Relation to B o hem cal Fact s

Since Mia nikow (1851) many in vestigators have reported that choles terol is higher in those of tocky than lean body build This has recently l een uggested as an a sociation with body fat rather than muscle (Key A Ander on J T Fidanza F Keys M H and Swahn P Clin Chem 1 31 52 (Feb) 1955) (Miller D C Trul on M F McCann M B White P D and Stare F J Diet Blood Lipids and Health of Italian Men in Bo ton Ann Int Med 49 1178 1200 (Nov) 1958) and (Tanner J M J Physiol 115 371 390 (Dec) 1951) To dis tingui h fat from muscle Keys and Miller u ed kinfold Tanner u ed both skinfolds and somatotype

The consistent relation hip noted be tween body fat and erum cholesterol is low with a coefficient of correlation at best 0 40 though tatistically signifi cant However muscularity of build said to characterize persons particularly su ceptible to coronary heart disea e has with equal consistency hown no relation whatever to erum chole terol level This is puzzling in view of the well documented elevation of erum

chole terol among patients with coro nary heart di ease Perhaps Dr Spain hypothesis of a lower thre-hold for athero clerosis among mu cular persons *afford an explanation* More re earch is obvious ly needed on this point

(3) R latio t Occ pat on a d Phys cal A t ty

Since Morris work (Morris J N Heady J A Raffle P A B Robert C C and Park J W Lancet 2 1053 1057 (Nov 21) 1953) on British bus drivers and conductors and on postmen and telegrapher occupa tional differences in coronary heart di ea e have been attributed to energy expenditure However there is a real possibility that self or job selection re sult in a concentration of certain type phy ical or constitutional in certain occupations Morris him-elf recognized this possibility finding that bus drivers had larger waists than con ductors on entering ervice with the bu company (Morris J N Heady J A and Raffle P A B Lancet 2 569 570 (Sept 15) 1956) I revious indepen*dent work on American bu and truck* drivers howed that they were more mesomorphic and tockier than the gen eral population (Damon A and Mc Farland R A Am J Phy Anthropol 13 711 742 (Dec) 1955) The same authors indicate that const tent physical differences have been reported among occupation and adduce evidence that the e are not cau ed by the occupation (Damon A and McFarland R A J A M A 153 622 625 (Oct 17) 1953)

In a recent letter Dr Morris informs us that further analy is of morbidity and mortality data among bus drivers hows plenty of heart di ea e among both fat and thin However fat drivers have more heart disea e than fat con ductors and thin drivers have more than thin conductors Here again i an area which needs further tudy

B *Methods for Obtaining Information*

Descriptions of body form for study ing correlations with cardiovascular di ease are obtained from height weight and other anthropometric di men ions skinfold thickness somato types strength tests and physico chemical analy es of body compo ition The last four techniques attempt to sup-plement the u eful height weight rela tionship by apportioning total weight or bulk among various ti sue and com partment particularly distingui hing mu cular bony from fatty components

(1) H ght d We ght

Height and weight are minimum e entials and should be taken as nearly nude as po sible The practice of per mitting light clothing and footgear has vitiated everal large and expensive tudies If ome clothing mu t be worn —and ock hort and bras iere may have to be permitted—several represen tative clothing amples should be weighed to give an accurate subtraction constant

These basic dimen ions should be taken with the care expended on the *ECG* and *cholesterol* determination Sloppy technic l y untrained or unsuper vi ed technicians is all too common

Height should not be taken with the bar attached to some medical balance cale but preferably again t a flat wall without a molding at the ba e with the subject in tructed to stretch to his maximum height and to take a deep breath Printed engineering trips ruled in inche and tenth or in centi meter are satisfactory for pa ting on the wall A cigar box or other right angled block can be lid down the wall until firm contact is made with the head oriented in the horizontal eye-ear plane (top of external auditory meatus and inferior margin of bony orbit) If a scale bar mu t be used it should be calibrated fir t and again the subject urged to tretch and tapped in the lum

bar region to facilitate thi An an thropometer is acceptable but only in the hand of a trained person

Weight hould be taken preferably on a medical type of balance scale to the nearest pound height to the near est millimeter on an anthropometer tenth of an inch on printed strips or quarter inch if the scale bar is so cali brated

Almost as important as current weight is weight hi tory as detailed as possible Inquiry hould be made—and checked by objective records if po sible—as to maximum weight age when attained its duration and cau e (in activity illness pregnancy) rea on for weight loss if any and duration of cur rent weight It would be desirable to reconstruct weight during each decade of adult life Weight can often be re called in connection with athletic par ticipation military service marriage or pregnancy Each figure should be pecified as with or without clothing Of course such ubjective data involve considerable error A rough check on reliability is afforded by asking the subject his current weight before weigh ing then comparing the two figures

(2) Index of Body B ld

U e of the data once obtained is not strictly within this subcommittee s pur view but the utility of the ponderal index height/cube root of weight, as a simple generalized description of body build is worth noting Though not dis tingui hing between the fat and bony mu cular components of body bulk its distribution is known in several izable population amples and promising correlations have been reported with occupational choice physiology and di ease Attention should al o be drawn to the widespread but unfortunate cus tom of expressing perfectly good nude heights and weights as perce ntages under or overweight based on clothed standards of dubious applicability to the populations being studied

(3) Skinfolds

These are u eful correlating about 0 70 with body fat and with endo morphy An excellent in trument the I auge skinfold caliper is available from the W enner Gren Aeronautical I aboratory of the University of Ken tucky

The two preferred sites for mea ure ment are triceps and subscapular Technic is extremely important ince slight variations in method and location of site can make major differences in readings The technician mu t be trained and at least initially checked by a skilled professional The ame tech nician should take all the mea urements in a given urvey if possible

(4) Circ mferences

Upper arm circumference at the level of the skinfold chest circumference (in males) waist circumference eat (hip) circumference and maximum calf cir cumference are desirable Of these only the first is recommended a a minimum essential (but ee below) by the National Research Council Commit tee on Nutritional Anthropometry (Brozek J Body Measurements and Human Nutrition (Ed) Detroit Mich Wayne Univer ity Pres 1956) These are all horizontal with minimal pre sure and made with a millimeter teel (not cloth) tape Keuffel and Esser Wyteface or Lufkin All cir cumferences are measured three times as are skinfolds recording the best single figure Chest circumference is mea ured during quiet breathing

(5) B acromial and B I ac D meters

Though recommended by the NRC *Committee on Nutritional Anthropome* try and though theoretically useful in indicating laterality of build these two skeletal dimensions alone have so far proved much less relatable to behavior

physiology or disease than ratings of morphological masculinity and femi ninity based on additional criteria Thi is true whether these dimen_ions are analyzed separately added related to tature separately or combined or when related to one another as an index of morphological masculinity (Seltzer C C Psychosom Med 8 75 97 (Mar Apr) 1916) (Damon A and McFar land R A J A M A 153 622 62ɔ (Oct 17) 1953) (Miller D C Trul son M F McCann M B White P D and Stare F J Ann Int Med 49 1178 1200 (Nov) 1958) Further more they require anthropometric kill and are worse than useless unless so taken Since these measurements are currently being taken in several ur veys it may be premature to di card them until all the evidence is in For the present it seems be t to retain them along with upper arm circumference as on the borderline between minimum ac ceptable and desirable until their value is proved or disproved

Unless biacromial and bi iliac di ameters can be measured accurately and reliably which requires training they should not be taken at all

(6) S H ng He ght

This is a desirable measurement, since it varies with sex race and body build and since—by subtraction from stature —it provides a mea_ure of leg length a u eful tailoring dimension along with che t waist and eat circumferences In retrospective studies such as those current at the Johns Hopkins and Al bany Medical Schools (Paffenbarger and Krueger this conference) clothing size may provide data not otherwise available on body dimensions With height and weight such data permit an approximation to body build

(7) H nd Gr p St ngth

This correlates about 0 57 with fore arm girth largely mu cle (Landegoard II Acta p ychiat et neurol Suppl 86 pp 1 163 1953) Strength may also be relat d to energy expenditure

(8) Photographs

These provide a permanent record of what the subject looks like From photograph reliable measurements of body diameters can be made especially if the anatomical landmarks have been marked on the subject One may also obtain somatotypes hair patterns mas culinity rating and planimetric de termination of body areas and even volumes if front side and back poses are available Since the strongest evi dence for an as ociation between body form and coronary artery disea e comes from somatotyping it seems logical to recommend this photographic technic (Sheldon W H Varieties of Human Physique 1940 Atlas of Men New York Harper 1954) Other photo graphic technics may be as good or bet ter but none has received so extensive a trial (Tanner J M and Weiner J S Am J Phy Anthropol 7 145 186 (June) 1949 and Gavan J A Wash burn S L and Lewi P H Am J Phys Anthropol 10 331 353 (Sept) 1952) The important point i to photo graph at a tandard di tance with a known magnification factor and with the subject carefully posed in the three tandard views A 90° turntable is desirable

(9) Res arch T hn es

Research technics well worth investi gating but not as yet suitable for epi demiological studies include method for analyzing body composition in the liv ing uch as den itometry gas and dye dilution body water partition and radiography (Key A., and Brozek J Phy iol Rev 33 245 325 (July) 1953)

The ultimate logical tep is to study the mechani m underlying tho e as ociations between body form and cardiova cular di ea e which with fur

ther work remain firmly establi hed One such research area being studied by Dr Spain is the correlation between body build and endocrine statu Another is the correlation between body build and organ or ti sue morphology

Summary

Subject to later revi ion if warranted by experience the following mea_ure ments of body form are proposed for epidemiologic tudies of cardiova cular di ea e

Minimum Acceptable Measurements

Height
Weight –plus weight h story in as much detail as pos ible
Sk nfolds—subscapular and triceps
B acromial and bi liac diameters
Circumferences—upper arm chest (in men)

Desirable Measureme ts

Seat wai t, calf c rcumferences
Sitting height
Hand grip tren_th —Collins-type dynamometer carefully al brated Narra ansett Gym nasium Equipment Co Centralia Mo
Photographs—front side and back po es.

Conclusions

(1) We reiterate that when physical activity is of concern in epidemiologi cal tudies knowledge will be required of average daily energy expenditure the pattern of activity as regard peak levels and timing and the phy ical environ ment in which activity is performed—all over a period of years

(2) In many tudie it will be de irable to know the phy iological re pon_e of our populations to physical activity in terms of cardiovascular strain involved in performance of accustomed activities and of a tandard work ta_k The best available single index of effec tive cardiova cular capacity is maximum rate of oxygen uptake (or the energy equivalent of such uptake)

(3) Our definition of energy expen diture levels in terms of light moderate and heavy with caloric expenditure levels designated for each is useful in epidemiologic studies The description of the tandard man to whom such caloric values apply and a method of finding the equivalent caloric values ap plicable for nonstandard men are pelled out

(4) When fea ible record of diet ary intake hould be u ilized to check estimates of total energy expenditure ob tained from analysis of phy ical activi ties

(5) The cardiova cular tress of physical activity may be more directly represented by an index which utilizes heart rate and blood pressure than by an index of caloric expenditure In other word energy expenditure does not always reflect heart work How ever one mea ure is not a sub titute for the other When an hypothesi call for investigation of relation_hip between heart work per se and degenerative CV changes a heart work index will pro vide the information that is most di rectly relevant However when bio chemical or phy ical concomitants or by products of muscular action are being examined in relation to cardio vascular change energy utilization is the information that will be most di rectly u eful

(6) We reiterate that minimum ac ceptable measurements neces ary for description of body form are height weight (with hi tory) skinfold thick ness and key circumferences and di ameter Such information on mor phology hould probably be a matter of record in all tudies of concern to this conference The information will of course be es ential in studies where the focus is on diet or activity Other measurements of the given li t are desir able when it is fea_ible to obtain them

Recommendations for Research on Methodology

(1) Method should be ought for determination of blood pres ure durin, work This would enable derivation of u eful indexes of heart work based on appropriate combinations of heart rate and blood pres ure values

(2) Methods should be developed for monitoring and recording blood pre ure and heart rate over ext nded period This would give information of value in judging cardiovascular cost of the complex ta ks which make up a day s activity

(3) The reliability of information obtained by various technics of ques tioning and interviewing on physical ac tivity should be verified by direct ob ervation

(4) Means hould be developed and validated for predictin maximum oxy gen utilization without requiring maxi mum work First efforts should be di rected toward finding the reliability of prediction of maximum work capacity ba ed on phy iological respon es to sys tematic increa es in work load from light to moderate

(5) Stati tical procedures for work samplin, should be developed a a means for determining energy require ments of various occupations

APPENDIX 1

Outl ne of Method for Measu ement of Ph y cal Act v ty (with Key Reference)

1 Energy Expenditure (respiratory volume oxygen utilization)— Estimate from oxygen consumption (with or with out CO production) Method involves metering of expired air collection of total volume or aliquot sample mea ure ment of oxygen content (CO content) computation of energy consumption as oxygen utilization x 4 9 (approximate) =calories ener, y Weir has provided a refinement of computation which takes protein metabolism into account [1]

I recautions : Arrange apparatus to encumber subject as little as possible In de cribing energy requirement of a task obtain repeat mea urement if possible on different subjects Attempt at showman hip on part of subject can markedly alter level of activity and timin of ta k to point where repre en tative value are not obtained For high level activitie mea ure O uptake by the o called integral method at rest before and during work and recovery o that anaerobic a well as aerobic co t of effort may I e asse ed Cost of work depends on the mu cle groups in volved energy co t of locomotion de pend more on body mass than surface area so expression in KCal per unit weight is preferable

(a) Classical method nvolves collection of exp red air in Douglas Bag or sp rometer later meter ng and collect on of sampl for analysis, analysi ot sampl for O2 and CO with Hal dane apparatu [3 4]

(b) The Max Planck In titute at Dortmund has developed a device [5 6] which meters ex pired a r w thdraws 0.3 to 0 6 per cent of total for analysi Dev ce requires cal bration at ariou rates of air flow

(c) Wolff has d veloped an integrating Motor Pneumotach g aph (IMP) [7 8] for meas uring volum e and collect ng sample It is the h htest device available a d h s been used continu usly for period, of ma y hours Samplin pe iod should be more than 10 m nutes

(d) Paul n, [9 10] has de elop d s mple me ns for determ nation of O n expired air depending on pa ama net c prop rties of ga es. Dial reads dir ctly in per cent or par tial pressure of oxygen Fa t r and requi m les skill th the Halda e method a curacy i suffi ent but ot a good as Hald ne

(e) If qu d CO n expired air can be alyzed l y inf are l gas analyzer [11]

(f) Time we ght n of indi dual tasks w ll u ually be necessary to d rive valu for total e rgy o t of jol F ample of procedures s p ovid d by Morris [1]

2 Pul ■ Rate

(a) By manual palpation Radial pulse may not be accessible without disturbing work in which case carotid may ■e convement site of palpation Po texertional pulses have meaning for certain tests of fitness but should not be relied upon as index of grade of work *previously performed*

(b) By EKG or cardiotachometer Heavy muscular efforts and sweating make accurate measurement by these means diff cult. Use of chest lead helps reduce static"

(c) By pickup from photensensitive element which follows changes in opacity of the ear

(d) A general reference on these systems is provided by Dill[13]

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APPENDIX 2

Check List of Items to Be Covered in Que tionnaires on Phys cal Activ tv

Off the Job Activities
- Routine current activities—hours and maxi mum effort
- Regular exercise—sports walkin„ ama teur professional competition
- Home maintenance
- *Hobbies*
- Transportation (walking to work etc)

Attitude toward exercise
Amount of sleep
Hi tory of phy ical activity
- School and college changes since—relate to wei„ht history

On the Job Activities
- Present job—duration
  - Hours vacations lay offs
  - Title
  - Job description—what do you actually do
  - Maximum efforts—rest periods—periods of intense activity
  - Proportions of sedentary standing walk ine climbing etc
  - Heavy lifting—Heat stress
- Previous jobs—general type and details as above—p riods of unemployment
- More than one job
- Attitude toward job

SUBCOMMITTEE ON BIOCHEMICAL MEASUREMENTS

Forrest Kendall Ph D Chairman

THE Subcommittee on Biochemical Measurements considers that its task in this conference is

I To discuss the place of biochemical measurements in epidemiological studies of cardiovascular diseases

II To set up criteria for judging the suitability of any specific biochemical measurement for such a study

III To outline the procedures required to achieve comparability of measurements made in various participating laboratories throughout the duration of the study and

IV To recommend a plan for implementing a system of controls necessary to achieve this comparability between laboratories

I The primary purpose of any epidemiological study is to evaluate the influence of diverse genetic and environmental factors upon the occurrence and severity of a disease We all recognize that the achievement of this purpose in the field of cardiovascular disease is of the utmost importance and of the utmost difficulty This is particularly true for atherosclerosis and hypertension No one has succeeded in demonstrating specific etiological agents for these diseases However marked differences in the occurrence and severity of these diseases in different population groups support the hope that epidemiological studies may succeed in defining the factors which cause them Two obvious difficulties of applying epidemiological techniques to the study of these diseases are the chronic character of the diseases *and their presence in* occult form in a considerable portion of the population Factors leading to the development of these diseases may be operative over a period of many years before clinical manifestations are recognized

The problem would be simplified if it could be shown that a cardiovascular disease produces some characteristic biochemical change which appears before clinical symptoms become manifest and which disappears when the cause of the disease is removed Much research in the field of atherosclerosis has been undertaken in the hope of showing that the concentration of some substance in the blood is as useful diagnostically in this disease as the level of glucose is in diabetes mellitus The presence of abnormal deposits of cholesterol and other lipids in the lesions of atherosclerotic arteries has focused attention upon the relationship between serum lipid level and the presence of diagnosed atherosclerosis Studies have been made of the relationship between coronary atherosclerosis and the serum level of cholesterol of phospholipid of cholesterol phospholipid ratios of alpha and beta lipoprotein of triglycerides and of chylomicrons Some degree of correlation has been found to exist between the level of each of these factors and the disease Although the differences between the mean levels in diseased and control groups are statistically significant the values for the two groups are distributed over very similar ranges and have little diagnostic or prognostic significance for any given individual

It is interesting that this statement could have been made immediately after the publication of the first study of the *distribution of serum cholesterol levels* in the serum of patients with coronary heart disease and a control group It was shown at that time that the serum

chole terol values were di tributed over similar ranges in both groups although the di tribution curves tended to be kewed in favor of high levels in the coronary patients Sul sequent surveys have only erved to confirm the ori,inal ob ervation they have added more points on the curve but the curves have not changed It i unlikely that addi tional work to increase the accuracy of the methods for either ampling the population* or of determining the serum cholesterol levels will add ubstantially to the usefulness of serum cholesterol levels as a means for diagno ing the pre ence of atherosclerosis Surveys that seek to relate biological levels with the disea e are not strictly epidemiologi cal tudies in pite of the fact that large groups of the population are being surveyed They still remain in the category of clinical investigations be cau e they do not relate the disease to pecific environmental or genetic factors which characterize the population under investigation The biological level of a substance in an individual is not neces sarily a characteri tic of that individual but may reflect environmental factors

In many studies a biochemical de termination ha been ubstituted either for an adequate tudy of these factors or for an adequate appra al of the clinical manife tations of the disease This procedure i valid only if it is known with certainty that the di ease is directly related to the biological level of the ub tance mea ured

At the present tage of our knowl edge the a umption that the biological level of any ub tance i an etiolo,ical factor in the development of athero sclero is may obscure rather than illu minate the si,nificance of an epi demiological tudy Thu populations consumin, high fat diets tend to show an increa e in serum lipid level as well as an increa ed incidence of coronary athero clerosis These two phenomena may be related to each other only by occurring simultaneou ly in many indi viduals The high serum lipid levels may be a direct result of the pre ence of large amounts of fat in the diet, while the development of the lesions may be due to ome other environmental factor which varies i tematically with changes in the fat content of the diet

An epidemiological study should be o designed that the biochemical data are not introduced into the scheme of the study as an intermediate factor B a ociating A the environmental and genetic factors with C the di ea e

A → B → C

Evaluation of a possible relationship between B and C may be one of the pur po es of the study but the survey should be et up in such a way that the effect of A upon B and C is a ses ed inde pendently

The placing of chole terol between the environmental factors and the disea e has resulted in a widespread tendency in the medical profe sion to treat the hypercholeterolemia in their patients as though they were treating athero sclero is It has been found that various types of medication will result in a re du tion of serum chole terol levels Nicotinic acid for example will reduce the serum chole terol level and many other thing will do it equally well Ep om salts is as effective perhaps as nicotinic acid Persi tent diarrhea re duces serum cholesterol levels very well indeed but does it cure athero sclerosis?

An out tanding ci ntist recently made the statement that he thought our preoccupation with erum cholesterol

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*Choice of population samples for study of atherosclero is poses many prol lem General populations are depleted by deaths due to atherosclerosis and other di ea es but include many person who have athero-cl ro is without clin cal manifestation B tt r diagnostic tests would simplify sample select on.

levels had resulted in the most flagrant example of tubular vision he had encountered in the field of medicine and that he felt sure that this preoccupation had prevented us from seeing and recognizing relationships that certainly existed between environment and the disease

It is possible that the most valuable function of biochemical measurements in studies of this type is to permit the selection of certain segments of the population to be subjected to a far more complete analysis than can be applied to the whole population Thus studies of the background of the individuals who develop symptoms of coronary atherosclerosis in the presence of low levels of cholesterol and beta lipoproteins in the serum or of individuals who do not develop symptoms of the disease in spite of persistent high levels may succeed in helping to define the epidemiological factors responsible for the disease

II To be useful in an epidemiological study a biochemical measurement must fulfill certain minimum requirements

(a) The level of the substance measured should not be subject to wide fluctuation dependent upon factors which cannot be controlled under the conditions of the study To cite an example The level of the unesterified fatty acids in the blood which may turn out to be a very important factor in this disease process is dependent upon the dietary intake physical activity and emotional status of the subject that study of this important biochemical factor could not be expected to yield significant information in an epidemiological study without extraordinary care in setting up basal conditions

(b) The concentration of the substance in the biological sample should not be subject to significant change between the time the sample is collected and the time when it is analyzed This would perhaps rule out many determinations which might yield valuable information if proper preservative techniques are not available This is particularly true of the concentration of various enzyme substances in the serum

(c) Analytical methods must be available that will yield reproducible results under all the working conditions likely to be encountered geographically throughout the study Some methods which are satisfactory in temperate climates fail completely under abnormal conditions of temperature and humidity

(d) The method elected should give valid results over the entire range of samples that might be encountered Thus some methods for the determination of serum cholesterol levels yield invalid results when applied to lipemic or hemolyzed sera or to samples where the concentration lies outside a small restricted range

(e) The method selected should be one that can be performed with technical adequacy by the laboratory personnel available Many methods which yield reproducible results in the hands of a highly skilled investigator are too difficult for the average technician

III The problem of insuring comparability of biochemical measurements made at different times and by different laboratories is not solved by the selection of a valid method Reports comparing the values obtained by different laboratories for the concentration of various serum constituents in replicate samples of the same serum reveal that intolerable differences occur unless systematic effort is made to insure comparability This difficulty is not one that is unique to epidemiological studies It exists wherever biochemical measurements are made It may be due to internal factors existing in individual laboratories that result in failure to obtain consistent results from analyses performed on the same sample on different days It may be due to external factors leading to differences in the analyses performed by the various participating laboratories Precise informa

tion concerning the cause of these difficulties is urgently needed

In 1958 the National Heart Institute and the Communicable Disease Center initiated a pilot standardization program with the cooperation of five laboratories interested in epidemiological studies The purposes of this project were (1) to investigate the usefulness of statistical methods for the detection and control of factors which contribute significantly to variations in total cholesterol values within and among laboratories and (2) to determine the practicability of using lyophilized human serum as a standard reference material for total cholesterol determinations The study showed that statistical analysis of the results obtained by introducing a small number of previously analyzed samples in each day's workload permits rapid recognition of failure to achieve internal reproducibility

The participating laboratories analyzed duplicate samples of lyophilized serum from each of four serum pools containing graded concentrations of cholesterol The analyses were repeated every three weeks for a 15 week period In this time three of the laboratories did not differ significantly among themselves The fourth consistently reported higher values than the others No secular changes were observed These results suggest that lyophilized human serum can serve as a reasonable reference standard

IV Up until the present time every epidemiological study has had to find an independent solution of the problem of insuring comparability of biochemical measurement The committee is of the opinion that the time has come when it would be economical for the organizations that sponsor this conference to take some action toward setting up a system to help achieve this comparability We believe that this would be done best by the establishment of a central laboratory which would have the following five purposes

1 To act as a central intelligence agency in order to maintain communication between laboratories and interested organizations carrying out specific measurements

2 To prepare characterize preserve and distribute standards which can be used in the calibration of particular methods This is a particularly important function that should be taken over by a central organization We all remember how a few years ago the service performed by the Bureau of Standards in providing accurate primary standards in many different fields of analysis played an important role in the development of chemistry in America This function is no longer necessary in most fields but it is still needed in the field of biological chemistry It may not be possible to buy a sample of cholesterol that is pure enough to depend upon as a working standard for the determination of cholesterol Each individual laboratory seems to be expected to know just how to prepare this necessary primary standard from commercially available cholesterol Provision of a cholesterol standard would help obtain comparable results from different laboratories Trustworthy standards are even more important in other fields e g reliable standards for measuring prothrombin time If this central organization did nothing but provide standard materials to enable the participating laboratories to check their results, it would serve an important function

3 To furnish consultative advice on biochemical method to interested and qualified laboratories

4 To compile and publish the experience and performance records of calibration studies

5 To act as an international clearing house for the exchange of biochemical information pertaining to the solution of methodological problems

COMMITTEE ON CULTURAL, SOCIETAL, FAMILIAL, PSYCHOLOGICAL, AND GENETIC INFLUENCES

Harry Kruse M D F A P H A Chairman

Introduction

THIS committee of the Conference on Methodology was concerned with cul tural societal familial psychological and genetic influences in relation to cardiovascular disease This postulated association is commonly based on the following as umption cultural societal and familial situations may create stress in the individual leading to or adversely affecting cardiovascular disease Why some persons react pathogenically to stress and why only certain of them have their cardiovascular system in volved are questions usually explained by attributing this electivity in part at lea t to genetic influences

Implicit in this hypothesis is the be lief that stress may either contribute to the development of coronary disease or at least, adver ely affect the clinical cour e of the e tablished disease Al though at present there appears to be no con ensus on the relevance and im portance of stre s in heart disease this po sibility must continue to merit con sideration until tre s and its related circum tances have been demonstrated unqualifiedly to have little or no sig nificance

Unfortunately the concept of causa tion—and of tress for that matter—may be so vague or oversimplified as to be mi leading Today cau ality of di ea e is eldom visualized in the old simple relation hip that A produces B Rather a holistic concept of cau ation envisioning a constellation of diverse factors is held Essentially these factors fall into three main groups (1) tho e in the environment using the term broadly to cover both the physical and social environment (2) those in the host or individual and (3) those as sociated with the adver e agent or process whether it be an exces a de ficiency or an interference The multiple individual factors subsumed under these headings vary in their on et rate intensity and duration Thus they have their own particular characteristics and functions in the con tellation and make distinctive contributions to causa tion Various names have been proposed to designate their characteristics and functions for example predisposing provoking precipitating perpetuating and conditioning factor and antece dent circumstances These names are of course not equivalent But one of the most important points to be borne in mind is that a factor that alone cannot produce a disease can determine whether the di ea e is produced With that in mind it should be obvious that, in the present tate of knowledge the flat statement that tres has a minimal ignificance in heart di ea e is erro u ly mi leading Until it has been irrefut ably demonstrated whether stress is an active component in the cau al con tel lation and until the nature and extent of its participation have been clarified it i impo sible to evaluate its ignifi cance with finality

In it nature and its expanse the sub ject of this committee po e ses charac ter tics unlike that of any other com mittee of the conference First, it com

pri es varied topics each of which falls under a eparate discipline Each discipline has its distinctive group of speciali t vocabulary and meth odology Second de pite this diversity all the topic in this subject are inter related For example here are natural pairs phy ical environment and the individual the group and the indi vidual omatic and p ychological en vironment and heredity The e pairs are interrelated not only horizontally but al o vertically and diagonally This complex interrelation hip poses a prob lem These topics are so clo ely as sociated that it is almost impo sible to discuss each eparately without some di tortion ari ing from incompletene s On the other hand discussing these in terrelation hips neces arily involves repetition Actually we hould talk on all points imultaneou ly But for pres ent purposes that procedure would create grave disorder

Third although this is a Conference on Methodology it was impossible in this section to exclude content The de sign of any study depends on its objec tive in turn both the design and objec tive depend upon a hypothesis which must be constructed from content Then too inclusion of content was even more es ential l ecause of the multidisciplinary as well a intradi ciplinary differences in subject matter terms and meanings In consequence this section had to be concerned with both the substantive and procedural pha e of the ubject

The basic assumptions of the subject its diversity the interrelations and mul tidi ciplines of its parts and the opera tional equence—all these considerations dictated the approach of this ection The ubject was divided into four major topics and the order of discu sion fol lowed the equence outlined in the hy pothesis describing their interrelation The e four broad topics were tre s en vironment (especially ocial environ ment) type of per on and genetics Thus the discussion started with the individual then moved to group phe nomena and finally returned to the indi vidual In each topic clarification and cry tallization of content was sought before methodology was discussed

From the standpoint of methodology it is useful to re tate at this point the sequence of events in the thesis to be investigated It is de irable to n certain whether cultural ocietal and familial influences produce stre s that may be linked with cardiovascular di ease A two tage operation would probably prove be t (1) the relation of cultural societal and familial factor to tress and (2) the relation of stress to heart disea e Of course it is pos ible to de vise a one stage operation which by pa ses stress namely the relation of social environment to heart di ease Such a study would doubtle s produce u eful data however if the evidence were po itive the essential intermediate steps would be mi sing

Stress and Adaptation

Because it occupies a central place in the cour e of events the tate of stress is the logical topic for first considera tion But there were also practical reasons Enough is known about stress to warrant the supposition that it can erve as a valuable indicator of influ ences to be looked for in the environ ment Furthermore *if stress is demon* strated to have any ignificant relation to heart disea e this fact becomes of utmo t practical significance in the pre vention and treatment of coronary disea e

In considering stress we are im mediately confronted with its meaning and the number of terms associated with it and ometimes u ed ynonymou ly strain load pressure tension It is by no means certain that stress is the proper term for the phenomenon under dis cussion but it would erve no u eful purpo e to cavil over terminology or to

draw distinctions in meaning Never theles its developmental history i informative

Twenty five centuries ago Hippocrate used the term stress in relation to di ea and in general the current biological concept is remarkably similar to his view In the late eighteenth century the concept of stres came into promi nence in phy ics in defining the proper ties of gases and olid bodie On the biological side Cannon brought tre s from the philosophical into the cientific realm by analysis of the biological re action His reaction test however wa limited From observations on experi mentally induced stre s Sely greatly ex tended the boundaries of the concept with his demonstrations and v ews of the alarm reaction general adaptation syn drome and local adaptation syndrome Wolff and Hinkle further expanded the concept and filled in missing areas by their tudies on the ocial environment its effect and man s reaction to it

Currently the term tre s is applied biologically to indicate the state in an organism which results from reaction to noxious stimuli or di turbing situations However the group expres ed ome re ervations over this interpretation In the group s opinion stre s itself is a concept combining both an abstraction and a generalization As an ab tract quality it characterizes a number of bodily states But the fact that tress i an abstraction is no rea on to avoid con sideration and u e of the term As it i usually described it is well recog nized Hence it wa agreed that as the term is u ed in biology and medi cine it ha understandable meaning man is facing difficulty To impart that meaning the term has u efulne It was decided however that it would not erve present purposes to attempt to differentiate and separate different type of tress such as acute or chronic emo tional or physical

It is useful to describe the nature of *stre s its meaning its production* the adaptive reaction which it elicits and its effects It cannot be overemphasized that the topic encompasses a eries of events with a potentiality for multiple processes at each tage

Man is exposed to two different kind of external environment physical and ocial Each in its own way exert its influence on him and each produces a different type of effect Here we are concerned with the di turbing not the beneficent influences

The physical environment including what we call nature has certain prop erties which affect man heat cold elec tric shock x rays pathogenic organi m and toxins By and large as a cla s they have a distinctive mode of rela tionship to the body of action and effects (1) They impinge directly upon the body (2) they di turb energy transformation by bringing about an increase or a decrease by withdrawal or interference and (3) they may de troy cellular form and function

Quite different is the ocial environ ment in its mode of affecting man Its influence ari es in ituations and per sonal interaction It is transmitted with out direct phy ical contact with the body Instead stimuli are received by man s en ory y tem Out of the mul tiple impul es in an experience ome are selected and ummated The ensu ing ensation arou a ociation mem ories and feelings In hort perception and evaluation occur As an ideational proce evaluation may not take place until some time after an experience U ually there is a succe ion of idea tional proce es with temporal projec tion both retro pective and pro pec tive memories other imagerie both imaginative and anticipatory and thought Meaning and value judg ments enter into the thought tate and feelings are aroused An attitude of di satisfaction may develop in an affec tive tate of unple a antne

In evaluating a situation man takes into account the demands upon him and in turn his needs urging satisfaction all organized in a setting of circumstances and conditions For a variety of reasons the person may regard a situation as unfavorable To him it may appear to be threatening alarming overdemanding restrictive frustrating conflictive or unsatisfying It is well to reiterate that whether a situation in the social environment imposes a strain on a person depends upon his conception and evaluation of it Similar situations do not have the same meaning for all persons Indeed, a situation rated by a detached observer as undisturbing may not be so regarded by a person involved in it The opposite strangely enough is equally true

To unfavorable influences from both environments the body responds Either a disturbing physical factor or social situation may act as a signal whereby the body reacts in an effort to neutralize overcome and nullify the unfavorable influence to avert its further operation and to restore the body to its usual state This is the process of adjustment or adaptation in which the body responds as a whole physiologically biochemically and psychologically i e through bodily function mood thought and behavior Depending on the type of disturbance the reaction is mediated at various levels of the central nervous system For signals from a social situation the brain acts as an adaptive organ directing the mitigating opposing *and restorative efforts of the body* Since all parts of the human system are subject to participation in this adaptive reaction the tremendous potential of the brain for altering bodily function and behavior can scarcely be overestimated

The capacity for adaptation is not the same in all persons hence success in adaptation is variable How well man reacts to a situation in the social environment depends in part upon his conception of it When he perceives a life situation as oppressive obstructive or unsatisfying he may not be able to make a favorable adaptation

Somatic and psychological alterations occurring during adaptation may lead to diseases designated diseases of adaptation Their production has been variously explained It has been suggested that they occur as a result of inappropriate or overly sustained adaptation Another view is that disturbances of bodily function mood thought and behavior which occur during periods of adaptive effort make possible appearances of disease processes which might not otherwise manifest themselves

Ackerman has described in detail his views on the psychological processes comprising adaptation and the sometimes pathological consequences Three levels of phenomena are involved in the interaction between the individual and society the structure of the environment interpersonal relations and the *inner psychic life of the individual* Personality and society cannot be considered apart Human behavior is shaped both by the organization of the internal forces of personality and the external forces of society Social forces do not operate in a human vacuum nor does personality exist in a social vacuum Social forces are mediated through that phase of personality which achieves expression in group relations Hence in studying social phenomena the most serviceable definition of personality is that which emphasizes the orientation to social *participation*

The functions of personality are oriented in two directions (1) toward the internal processes of the organism and (2) toward the social environment There is continuous interplay between the two relations Together they constitute total personality In its position of interchange with the environment personality has a relative unity

Society is the medium in which the

identity of a per on gradually emerges As the individual matures he achieves an identity which is at once both indi vidual and social He has an individual elf and a social elf The individual component of personal identity is rep resented in the more durable less modi fiable aspects of character tructure It is the core of the personality the more personal private relatively fixed aspect of elf It reflects behavioral tendencies which have been conditioned by inter action of biological di po itions and family environment The ocial com ponent of a person s identity is represented in the less durable more modifiable layers of character It is less personal less private less fixed It re flects behavioral tendencies which have been acquired later It is these relatively more external layers of character which permit the greater degree of penetra tion by ocial forces The social identity of a person reflect the continued inter dependence of individual and society For pre ent purposes we are primarily concerned with this ocial self ri pre senting those functions of personality which are externally oriented

Those operations of the social elf in the context of a given life situation may be called social role Social role is the intermediate between intrapersonality life and group behavior being that in tegrative a pect of the total per onality which is expressed in ocial action It implies the capacity of the per onality to make fluid changes in form in ac cordance with the adaptational require ments of the individual s po ition in ociety In a given time and social situation certain components of the total elf are mobilized into action and moved into a dominant position while other components are temporarily subordi nated In essence this is the process of social adaptation By definition ocial role is the adaptational unit of person ality in action

The psychic proces es and combined components of behavior make up the configuration of social role Orienta tion in this action pha e of personality presupposes a set of goals and values commensurate with the individual s posi tion in a given group The values which provide directives for social action are derived partly from the indi vidual personality and partly from group organization they are oriented toward both self and one s relations to other persons Their dual ori ntation involves (1) personal attitude toward one s individual triving and (2) quality of apperception of culturally dominant patterns of interpersonal re lations

Out of the orienting coordinating functions of personality and the ur rounding group forces there is crystal lized a specific pattern of action which is reflected in the form of a particular social role Some of the components entering into the integration are apper ception of patterns of interper onal re lations attempt to achieve gratification of inner need assertion or subordina tion of self compliance with or prote t against social pre sure effectuation of means for control of the environment election of particular defenses against anxiety an effort to find olutions to personal conflict projection of inner conflicts into the social role These components determine value orientation and the corresponding configuration of the ocial role

The relative success or failure of adaptation in a given social role is the re ult of coincidence or conflict between character di po ition and ocial environ ment There are numerou vicis itudes in the relation between ocial role and individual personality First it is as sumed that the normal per on ha the capacity to effect flexibly a variety of ocial roles in accordance with adapta tional requirements But persons vary in the extent of their repertoire and they may be required to a ume roles

beyond their range or out of character

Second the degree of p ychic distance between the individual and ocial elves is significant In emotional content the ocial role may be peripheral or central to the individual self hence it may have central or peripheral significance in relation to the individual s emotional life Such relations will determine the degree to which an individual s identi fication with a group is genuine or false spontaneou and healthy or forced and anxiety ridden

Third the imount of anxiety gen erated is influenced by the degree of harmony or conflict between individual identity and social identity The per on s inner concept of self either may coincide with the a pect of self projected into a particular ocial role or may clash with it In the event of conflict anxiety is generated with profound effect on social role It may induce increa ing in tability and a tendency to rapid change of roles Or it may induce increasing rigidity In either event adaptive efficiency is impaired Thus the personality performance in a given social role is affected by the rela tive harmony or conflict between the ocial expression of self and the inner valuation of self

In this proce s of ocial adaptation the individual may react to social pres sure in four ways compliance protest withdrawal new integration It is the latter reaction which i of particular in tere t New integration occurs when social pressures are overwhelming and exceed the individual s resources for phable adaptation Sometimes the di lemma of more than one role brings on the crisis This situation occurs when a person faces two antithetical roles and is incapable of a suming either or when he must perform two roles but their conflicting nature prevents per formance of them The consequence of the unre olved conflict between the emo tional content of antithetical roles i an adaptive breakdown of the characteris tic and usual social role Then the per on re pond with integration of a new form with di tinctive properties of its own Thi proce seems to occur in the development of the so called psycho somatic di order

Through physiological arrangement in the course of adaptive reaction any bodily function subject to the regula tion of the central nervous system might be influenced to a ignificant de gree That regulatory influence might be mediated directly by any of the nervous pathway by internal ecre tion or indirectly through changes in the over all behavior of the individual Al o the physiological changes brought about during adaptation to life situa tions may include release or production of conditioning factors contributory to the occurrence of di ease Hence the association between adaptive reaction and incidence of illness may be ex plained on reasonable ground This recognition of the adaptive reaction to a social ituation as either a precipitat ing or perpetuating factor in disease imparts to this relation hip an impor tance in prevention and treatment

Whatever the explanation di eases have been produced experimentally as the consequence of adaptation Simi larly incidence of illness in person has been associated with life ituations con ceived by the individual as disturbing and involving the adaptive reaction In one study it was found that at lea t one third of all episodes of illnes were in fluenced in their time of occurrence or in their cour e by the attempts of per ons to adapt to situation From this same investigation came the view that the majority of all occurrences of illness in adults are influenced to some degree by efforts to adapt to the ocial environ ment Hence it has been concluded that man s susceptibility to illness i to a large degree influenced by his relation to society

This conclu ion is not surprising inas much as the state of the host has long been recognized to have an influence on the occurrence of illne s Exposure and extreme fatigue are conditions be heved to be conducive to the occurrence of disease or to adversely affect its cour e Reaction to a disturbing situa tion surely al o repre ents an altered tate of the ho t

To carry the equence of events to completion it hould be stated that not all per on reacting to a situation con tract the same type of illness Just as a similar ituation does not affect all per on alike those who do react with an as ociated illne do not develop the ame disea e Although man s relation to his social environment exert a major influence on the occurrence and cour e of illne it has relatively little influ ence on the type of the di ease Rather the type of disease is believed to be de termined by various other influence (1) The physical environment and op portunity for exposure to particular pathogenic agents and conditions ex tant at that time and previously (2) the genetic constitution of the per on The variability in the e factor could be re pon ible for the differences in the type of disea e developed

Enumerating a few of the various disea es a ociated with adaptive re *action* uch a *ulcers colitis a thma* and cardiac di ea e probably brings the s ord psycho omatic to mind Actually no qualitative differences have been found between di eases in their relation to ocial adaptation Whatever differ ence may exi t appears to be quantita tive that i certain di eases appear to be more readily and therefore more fre quently and more profoundly influenced in their cour e by the physiological effects of adaptation than are other The e have gained the name p ycho omatic di ea e

Thi account pre ents a working hy pothe i that fits the available ob er vation It can form the ba is for establishing a number of objectives in investigations de igned to test the propo sition that a relation hip exi t between ocial environment phy ical environ ment genetics and coronary disease

Methodology—With this background the group turned to con ideration of ob jectives and the methodology most ap propriate for achieving them Specifi cally it di cu ed the detection of stres and means for mea uring its intensity When it is con idered that stress may be induced by a variety of mean that stre sors impinge or gain entry to the body at very different point that in reaction the body u es various y tem and proce ses—physiological biochemi cal and p ychologi al—it is by no means certain that tress is a imple homogeneous quality Certainly recog nition of its possible heterogeneity and complexity give no encouragement to finding a ingle te t let alone a quan titative method It wa agreed that tre s cannot be directly di tingui hed It was admitted therefore that there is no measure of the tate of stress per in the body

The problem was then approached by con idering the relations of tre One is the reaction to it Can tre s be de tected by its effects? Thi question wa di cu ed in different term namely *the measurement of inten ity of stre* by indexe or indicator Reaction to stres it will be recalled compri e numerou functional changes involving phy iological proce and behavior Some of the change have been pro po ed and used a indicators of tre Changes in metabolic rate blood pre ure pul e rate oxygen con umption l ood clotting mood or behavior were mentioned But it wa decided that none of these indexes mea ures tres Corticoid exretion and blood level were regarded as being more related to tre and therefore l etter indicators l ut their limitations were acknowledged

It was thought that extensive measurements of these indicators in relation to stress would not be productive In the opinion of the group there is no simple indicator which provides an objective measure of the intensity of stress It was pointed out that future research may provide such an indicator For example changes in the hypothalamus seem to be close expressions of stress But a method for evaluating these changes is *not now ready*

The group then turned to the antecedent relation to stress namely the factors producing it A test was cited in which type and load of work were used as indicators in measurement of stress

Hinkle proposed that a combination of both relations the antecedent tressor and the subsequent reaction be studied Here the tressor was designated the challenge It was proposed that the challenge be discovered in the constellation of circumstances in the environment both physical and social that this challenge be evaluated and that the reaction to the challenge be studied

In an investigation of the relation of atherosclerosis and hypertension to personality and the social environment the complexity of this area and the use of the term stress should not obscure the fact that the epidemiological methods here are essentially no different from those used in other medical studies At the start a hypothesis should be formulated about certain events or processes within the cardiovascular system which are thought to be relevant to atherosclerosis or hypertension and about the way that these processes may be modified by nervous endocrine or behavioral influences as the individual reacts to his total life situation As the dependent variable some measures of the cardiovascular reactions are used As the independent variable one can measure objective features of the life situation features *of the individual which indi*cate that he perceives a given situation in a certain manner or features of the individual (whether socially culturally or psychologically determined) which make it likely that he reacts to his life situation in a certain manner The experimenter counts classifies and seeks association as in any other epidemiological study

The same considerations of experimental design selection of sample and *reliability of indexes that apply in other* studies apply here The experimenter should try to avoid naive assumptions (such as that primitive societies are less complex and less stressful) He should try to classify like with like (and not to assume that Negro school teachers are the same as Negro laborers) He should try to call phenomena by their precise name (and not to call anxiety stress) He should try to report results in terms of observations (e g responses on a psychological test) rather than as conclusions or diagnoses (e g hysterical personalities)

With the help of skilled behavioral and social scientists specific answers to specific questions can be obtained

In the same vein Ackerman suggested that the psychosocial representation of stress might be approached operationally in the context of the individual functioning within the family the family within the community This approach requires procedures for systematic psychodynamic study of the ongoing interactional processes of the individual patient with his family group It is assumed that the individual patients would undergo traditional forms of psychiatric and psychological study Beyond that however there would be systematic examination of the family phenomenon its internal organization and external adaptation to the surrounding community The individual patient is then viewed as a living unit within that group Necessary to such an approach is a *dynamic concept of the in*

tegration of personality into required family roles The phenomenon of breakdown and illness may be seen both as a function of the individual organism and as a function of the familial organ i m Of pecial significance in this *connection is the relationship between* the emergence of illness and the inter play of individual and family group defense against anxiety

In an attempt to correlate specific *defen operations anxiety and omatic* pathology it is necessary to look into the conflict ten ion and anxiety arou ed by a threat to a person s in tegrity Perhaps particular configura tions of subconscious conflicts and frus trations may be found to be related to di ease But the experience of conflict alone is no index of functional break down with illness It is essential to note how man perceives a threat in a situa tion and how he considers which of his resources might be mobilized to protect him and control his tension

Every human being experiences func tional distress in a particular way Hence it no urpri to observe certain re actions in the inner organ system When there can be no relea e of tension in the voluntary mu cles it may flow over into the sympathetic and para ympathetic systems That an inappropriate kind of mobilization of defense agains t ten sion a failing type of mobilization Such inappropriate mobilization sugge ts that there might be a relation hip between *acting out and acting in* The phrase acting out ignifies a situation in which a per on is experiencing a con flict in a distre ing way he cannot cope with it and in an irrational and *inappropriate way* elements of that con flict pill over into society in such a manner as to get him into trouble be- cau e his action does not fit the social ituation Although the consequences may be unplea ant for the moment the individual has ucceeded in relieving the exce ive ten ion and has tabli hed an equilibrium for his internal life However it is possible to conceive of a situation in which the individual would like to act out but does not dare Such a ituation would elicit different types of defen e behavior some indicative of *well being* and some which are patho genic either p ychically or omatically or both It would be profitable to con duct tudies on the mobilization of healthy or pathogenic defenses and their *po ible relation to disease*

Pather than attempt to work out the sequences of changes in the development of coronary disease with special inquiry into stres Dr Selye would go directly to a tudy to determine whether ub tances found experimentally to protect animals from cardiopathy would confer a like protection agains t coronary di ease in man He reported his ex perimental observations recommending that they be put to clinical test Dr Selve a serted that combined treatment with certain teroid and electrolytes produces a cardiopathy characterized by necroses The steroid was regarded a a conditioning factor i e it condi tioned the heart for production of the cardiopathy by the electrolyte Among all steroids tested only certain corticoid had this capacity As a conditioner 2 methyl 9 chlorocorti ol (Me Cl COL) po se sed the highe t potency

Following conditioning of animal with the effective steroid certain electro lytes could induce the necrotic cardi *opathy Only certain sodium alts* pecifically monosodium pho phate o- dium sulfate and sodium perchlorate had this ability Other odium alts were inactive It was concluded that both the cation and the anion po e ed this sen itizing potency

Certain other electrolytes actually pre vented development of the necrotic cardiopathy when they were given imultaneou ly with en itizing electro- lytes to animal uitably conditioned i th teroid Among all the alt

tested pota ium chloride and magne sium chloride were the most potent protectors

In all experimental animals used—rat guinea pig monkeys and dogs—this reaction has been produced It is fair to as ume at least that a chemical mechanism for it exists in man

Di tinct from the cardiopathy pro duced gradually by the persistent action of corticoids plus certain activating odium salt is the sudden eliciting effect of tre Although pretreatment of rats with thre hold dose of Me Cl COL plus $NaH PO_4$ produced little or no cardiac damage sub equent expo ure to the stress of neuromuscular effort immediately elicited severe and exten ive cardiac necro es in all experi mental animal Under the same ex perimental conditions of pretreatment, various stre creating maneuvers simi larly induced a high incidence of myo cardial necroses Neither Me Cl COL nor stre alone produced cardiac ne cro i But after pretreatment with Me Cl COL alone i e without sodium alts numerou quite unrelated agent creating tres had a cardiotoxic effect Hence the eliciting action of stress wa regarded to be nonspecific The pre ipitation of infarct like myocardial lesions by sudden exposure to stressors is of pecial interest in view of its clini cal implications

After pretreatment of rats with Me Cl COL a *ingle intravenous injection* of papain extract produced myocardial necro es more readily than otherwise

It is highly significant that KCl and $MgCl_2$ are effective in preventin the various forms of cardiopathy produced by the following different means (1) corticoid and sensitizing Na salts (2) corticoid conditioning followed by ex po ure to various tres ors and (3) in travenou injection of a protea e These ob ervation rai e the hope that they may al o l e beneficial in preventing cardiopathies in man

It was stated very clearly that the experimentally induced cardiopathies do not reproduce all the histopathologic changes presently regarded as a ine qua non for the development of coro nary di ea e For example there is no athero clero is Hence pathologically none of the experimental cardiopathies in animals is an analog of coronary di ease in man

Nevertheless since both potas ium chloride and magnesium chloride exert protective action again t various types of myocardial pathology induced experi mentally by different means Dr Selye believes that this fact warrants te ting of their efficacy in preventing coronary thrombosi in man Furthermore it would be a afe and simple procedure There are three types of procedures commonly u ed in ascertaining etiology and treatment of a disea e (1) experi mental production of the disease u ually in anim ls (2) test treatment of the naturally occurring di ea e in man and (3) test prevention of the natural di ease If patient studies on the pro tective action of the electrolytes were undertaken the preventive type would provide critical data In addition o many lives might be saved that uch tests are ju tified even if the likelihood of success eems small

Environment Culture

Having considered tress we now *turn to its environmental source* It is obvious that both the physical and social environments may cause stre Becau e the influence of the phy ical en vironment was scheduled to be di cu ed by another section our attention was focused primarily on the social en vironment as a source of stre s Yet o intertwined are the two environ ments that the phy ical environment was mentioned at appropriate points

It mu t be remembered that ociety cannot be considered separately from personality Human behavior i haped

both by the organization of the internal forces of personality and the external forces of society Indeed the two are interrelated throughout life Environment has a molding effect on character structure which varies with the distinctive features of each society At each age level and at each stage of personality organization the environment requires distinct types of social function from the individual Hence social environment contributes to the shaping of adaptive behavior by determining the path along which the individual may successfully adapt to his surrounding It reinforces some individual drives and subordinates others Current factors in the environment influence the social level of personality integration and may even penetrate to the individual personality

The social environment is also the medium for situations which are the sources of stress But again the situation cannot be considered separately from the participating personality The situation derives its meaning from the participant's interpretation It has been found that a participant in a situation evaluates its stress provoking quality differently than does a detached observer It may have a meaning and significance for the participant that does not enter into the observer's evaluation Hence the problem becomes How may personalized stress creating situations in the social environment be detected and identified and how may their relation to cardiovascular disease be studied?

Specialization has brought about a division of the social environment into culture society and the family It is therefore most convenient to consider the nature and methodology of each division separately yet the three become commingled when any one is subjected to study

Culture comprises the customs manners way of life and conventional wisdom of the group This way of life includes innumerable details of behavior which represent the normal anticipated response of any of the society's members to a particular situation Norms of behavior and opinion constitute a culture pattern Culture as a whole is a more or less organized aggregate of such patterns It provides members of any society with an indispensable guide in all the affairs of life It would be impossible either for them or for society to function effectively without it It operates with a background of social approval and social pressure

There are many types of culture in the world Broadly speaking they differ in their homogeneity and implicity Even within national borders whether in sections or in smaller subdivisions such as district variants of the basic culture may appear Since the anthropologist in his studies is often concerned with the cultural homogeneity of a sample he sometimes has to separate population groups into subculture and even into further fractions Because of cultural heterogeneity studies in the United States were regarded as most difficult by the late Ruth Benedict New York City itself offers an impressive array of subcultures

Dr Shapiro emphasized that the most important property of culture is the learned patterns of behavior By that is meant the patterns that people live by the expectations they have in the behavior of other people in their own community These cultural patterns confer the ability to carry on a relatively large series of behavioral patterns in a semiautomatic way By providing a way of routine living these patterns spare man the necessity of constant decision Because once a pattern is established and expectation built up for most of the events in daily life man can proceed in a predetermined way without giving much thought to it This proce

dure is of course a saver of time and of emotional wear and tear on the individual for having to make fresh decisions for every item of behavior would indeed be time consuming and enervating Man comes to take his cultural pattern so much for granted that most of the time he does not think about its operation Then when he encounters a situation which is different he thinks of it as being very odd strange and peculiar

No matter how well regulated a society may be how well understood the cultural patterns may be by members of the community there is always a residuum of conflict which may arise anywhere in the social order to provoke emotional stress It was Dr Shapiro's belief that a highly educated society in which the people have a variety of rules and statutes to contend with may contain many more stress-creating situations than does a primitive organization For example being a member of a minority group or exclusion from a social class or operation of economic factors that are flexible and open to manipulation beyond what the cultures might be expected to control—all these things as they appear in the more highly developed society give rise to more situations which could produce stress than occur in a bushman society where there is not much economic distinction between the members of the society where there are no classes and where there are no minority groups Obviously even there some situations which would lead to stress would occur but the number would be fewer

Methodology—It is appropriate to describe briefly the way a cultural anthropologist works his methodological approach, once he has selected his population sample His objective is to provide an account of group behavior in all activities of living But such an area of observation is vast and complex Culture itself has a multitude of component each comprising numerous details To add to the difficulty an individual may differ in his behavior if ever so slightly from time to time and individuals may differ even more from one another Thus a real culture pattern is a series of varying behaviors although the range of variation is usually within moderate limits

This variability of behavior yields data that are much too bulky and unwieldy to be descriptive and workable Hence the anthropologist develops a culture construct pattern by establishing the mode of the series of variations within the effective range of a real culture pattern he then uses this mode as a symbol for the real culture pattern The total culture construct is obtained by combining all the culture construct patterns This procedure provides a concise and convenient approximation of the conditions existing within the real culture It is a serviceable method for summarizing group behavior in the activities of living

It has been repeatedly emphasized that whether a situation is stress provoking *depends on the conception of a person* involved in it not on the judgment of a detached observer Since the situation thus derives its value from the participant the anthropologist as a detached observer cannot directly unerringly and assuredly detect and identify stress bearing situations At best he can study each culture separately and select those situations that might be stress provoking

Cultural patterns of behavior are the concrete expressions reflecting generalized meanings or values Because of their influence on behavior value orientations play an important function in the lives of individuals Professor Clyde Kluckhohn defines value orientation as a generalized and organized conception influencing behavior of nature of man's place in it of man's relation to man and of the desirable and nondesir

able as they may relate to man environment and interhuman relations

Florence Kluckhohn has developed a conceptual scheme which will permit a systematic classification of cultural value orientations as they pertain to universal human problems. This scheme sets forth central types of value orientations and the ranges of their possible variability. It is based upon two assumptions. The first is that there is a limited number of basic human problem for which all peoples at all times and in all places have had to find some solution.

Five of these common human problem regarded as being of key importance were stated in the form of questions:

1. What are the innate predispositions of man? That is what is his basic human nature?
2. What is the relation of man to nature?
3. What is the significant time dimension?
4. What is the valid personality type?
5. What is the dominant modality of the relationship of man to other men?

The second assumption underlying the scheme is that solutions found for the problems are variable but that the variability is within a range of possible solutions. She recognizes three types of solution for each universal human problem. This scheme permits a systematic comparison of societies or subgroups on the basis of man's conceptions of fundamental and universal relationships.

Dr. Shapiro acknowledged the validity of the types of value orientations. However, he believed that their application in observations on individuals might be difficult because they are abstract. As a more useful procedure he prefers to deal with specific everyday situations.

Dr. Shapiro enumerated several examples of likely sources of stress in cultures. Mother-in-law avoidance in some American Indian societies is a custom which might be a source of stress, whereas in our society with its mother-in-law jokes the situation is not the same. On the other hand, social mobility is probably a source of much difficulty in our own society, but it does not exist in Polynesia. There the natives are not fired with ambition to become tycoons. Polynesia has no tycoons, so the natives have no particular desire to be one. Indeed, Polynesia has no social classes and corporations, hence it has no high pressure executives. Prestige and sexual jealousy occur in both cultures, but in quite different character. Certainly stress occurs in all societies. What should be underscored is that the origin of the stress may vary not only with the conception of the affected person but also from one society to another. *Even when societies are apparently* similar they may not be because of the different overtones.

Dr. Hinkle recounted observations from a cross-cultural study of health patterns in groups of Chinese, Hungarian, and American college students. Cultural differences were observed in their attitude toward work, relationship to father, and getting ahead. He raised the question whether the type of attitude might be associated with a cardiovascular reaction pattern related to the development of atherosclerosis.

Dr. Shapiro pointed out the danger of overgeneralizing on the basis of observations from a subculture. For example, getting ahead has a very high value rating among a very limited portion of the Chinese population. But it is by no means typical of all Chinese. Nor are all Americans driven by overwhelming ambition and high aspiration. Since there are subcultures in both China and the United States, it is risky to use subcultural patterns in making broad generalizations about Chinese and American. It is necessary to ascertain how general a pattern is in a culture.

Three other types of studies were re-

garded as likely to yield significant information

Because of inadequacies in published data it would be desirable to conduct cross cultural studies on blood pressure

Concerning hypertension it would be useful to study cultural groups in which persons have a desire to act out but fear to do so because of the consequences as contrasted with other cultures in which it is permissible to act out freely

Interrelationship normally provides the individual with some degree of protection In our society this system is not working as well as it might It would be helpful to study groups in which the culture normally provides varied degrees of reinforcement The individual should be studied in relation to the family and to the larger culture In this comparison of cultures possible relationships with cardiovascular disease should be tested

To Dr Shapiro the paramount question in methodology was how to evaluate stress in one culture in comparision with stress in another It is a difficult problem because the personal reaction appears to outweigh the particular situation For example is the Chinese boy striving for scholastic prestige under the same kind of tension and pressure as an American youth attempting to climb in a business organization? It is conceivable that the two situations require different types of adaptation Whether one might be associated with a significant change in cardiovascular function is a matter for testing Above all it would be helpful to have an objective physiological measure for evaluating the stress provoking potency of situations Then they could be more readily identified and compared in different cultures

Some caution should be exercised in the consideration of broad cultural factors associated with stress as possibly related to heart disease Specifically the following conceptions and practices are to be avoided

1 Lumping all threats or strain upon the individual under the encompassing term of load stress or challenge It would be better in any anthropological investigations to make observations on more limited and specific phenomena Fear rage dilemmas of decision ordeals of endurance or tolerance

2 Failure to differentiate as far as possible between the phenomenon of culture and the phenomenon of society For research purposes there is an advantage in keeping them conceptually and somewhat operationally separate

3 The popular and largely false assumption that the relatively primitive and preliterate societies are simpler and less stressful than are our sophisticated and civilized societies Their stressors may be more intense than ours and some of their components may be more complex (language kinship systems and so forth) We can be certain of finding wider cultural contrasts in primitive societies but not so certain of finding greater simplicity of components or potential stressors for personal experience

4 The easy assumption that culture and society are primarily offenders rather than befrienders to persons subjected to stress (fear etc) The primary function of culture and society is to solve or resolve a peoples problem Most sociocultural systems do a reasonably adequate job of it

5 A tendency to neglect or ignore the utility of a balance between stress induction and stress reduction mechanism within a sociocultural system (ghost fear)

6 Failure to properly differentiate between a homogeneous and stable culture and a heterogeneous and/or changing culture There is an apparent tendency for the reduction mechanisms of culturally induced stress to break down more rapidly than the induction mechanisms

7 Failure to recognize and account for the fact that culturally induced stress is subject to modification by the significant reference group members and

by individualized personal experience (family)

■ Failure to allow for or to take advantage of the phenomena of cultural selectivity in socially conditioned stress induction and stress reduction

9 Possible lack of adequate recognition and utilization of existing sociocultural variation in family size and structure

10 Possible lack of recognition of the research potentials of cultural variation for testing the hypothesis of acting out and acting in of stress frustration

Environment Society

Concurring in the statement that no societies are free from sources of stress Professor Simmons went even further in saying that it probably would not be possible for a society to survive without sources of stress As society's means to stimulate and control action stress has a survival function Professor Simmons described a procedure for identifying stress provoking situations by peeling off layers of perceptive interpretations of them A list of critical situations with a potential of creating stress in the life of man in his culture is prepared for a particular society Three questions are then applied to each situation Would it induce stress because of its physical elements? Is its stress-inducing nature reasonable only in the light of the culture? Is there any aspect of the situation provoking stress that is not explainable by either the physical environment or human culture and dependent upon the special experience and idiosyncrasies of the participating individual? In short these questions seek to ascertain whether the stress inducing nature of the situation has a basis of physical or cultural realism as shared by other members of the society

When applied to the Hopi Indians it was surprising to find little in the physical environment that served as a real stress source of stress Yet it was obvious that in their lives the natives experienced much stress mostly cultural in origin Certain situations also had stress productive aspects that did not seem to make sense Deeper investigation revealed that the natives had been conditioned to fear particular situations It was then possible to place much of the seemingly illogical and unintelligible in the category of culturally realistic stress bearing situation Furthermore it was observed that although the native are subjected to culturally determined stress potential their stress is resolved by other cultural provisions Thus the culture creates stress provoking situation *but it also provides protective measures* against them

From these observations Professor Simmons concluded that it is necessary to look searchingly into both the culture and the person's life history to discover what patterns conditioned his fear It may be necessary to slice the culture into such subcultures as occupational ethnic religious and familial aspects in a given society

The usefulness of social variables in society for epidemiological studies might be considered on the basis of their possible relevance to stress or cardiovascular disease e g the nature of the social system social status with processes of social stratification social interaction and social mobility and social roles whether they be ascribed achieved adopted or assumed

Other sociological variables used in various studies and found to be significant are social class type of residential area occupation identification in the general population authority leadership responsibility and affectional ties To these may be added the following variables size of group forms of internal communication rules determining right of members method of assigning tasks and handling grievances

A program of sociological research

into the epidemiological factors possibly associated with cardiovascular diseases might profitably follow the plan which is outlined by Dr Simmons with steps taken somewhat in the order named If undertaken by sociologists it should be under the constant counsel *and guidance of a medical team of per*sons who are recognized as experts in cardiovascular disorders

A general ecological approach would be recommended as preferable particularly in the initial stages of the study Study should be concentrated on a particular geographic area containing a reasonably wide range of factors suspected to be significant in predisposing persons to cardiovascular disease In addition the factors considered (biological social cultural familial psychological etc) should be those for which fairly reliable techniques of differentiation and/or measurement are available It would also be preferred that an area where a considerable number of good ecological studies have already been made be chosen in order to take advantage of the accumulated ecological knowl*edge existing on the area Good examples* would be New Haven Conn Providence R I Framingham Mass or Evans County Ga Other areas might be selected later to serve as areal controls or for comparative purposes The chosen area should be sufficiently representative to make possible the gathering of data on the various factors listed below or at least a selection of them

A representative sample should be taken of the entire population of the area as of a specified date This sample would serve as the base line and population from which all the succeeding data would be drawn for analysis and correlative test

Every member of this sample (with provision for substituting members for drop outs or those failing to cooperate) should be subjected to a competent medical diagnosis to determine the presence of cardiovascular disease both in clear cut instances when there is no doubt of the actual presence of the disease and in cases of border line incipient or potential existence of the disorder Others should be medically identified as clearly free of any recognized symptoms or in*dications of incurring the disease* These would serve as controls or for panel or cohort studies in long term perspective The ill and potentially ill would be classified according to degree or type of complication age and other categories to be studied as the research progressed Probably special attention would be given to the middle aged and younger categories and only general attention paid to the aged persons

Some order of priority or sequence should be established in the making of statistical checks on incidence or prevalence of the disorders as correlated with existing social factors. An order such as the following might be followed sex racial or ethnic grouping rural or urban residence ecological areal placement in the region studied immigrant generation religious affiliation social *class position as specifically or operation*ally defined—family structure stability and status as operationally defined extent of social mobility as operationally defined etc

When these gross statistical correlations have been carried as far as feasible on the basis of findings intensive interviewing of stratified sampled and perhaps paired respondents should begin for much more detailed and definitive studies These could be made on a one shot cross sectional basis and on a long term periodic panel basis Such factors as shifting age status economic stability family equilibrium social mobility diet stress components and so forth could then be studied in the context of case history and life history as well as the sociological context

This is perhaps as far as it is at all useful to suggest possible design for an

ecological study Next steps all along the way would be influenced primarily by the findings from the steps previou ly taken

Environment Family

In the va t social structure a key unit is the family It is a primary group intermediate between the individual and wider society Here in this smalle t and clo e t ocial group culture, society and the genes meet Family bond are made up of a fusion of factors biological p ychological social and economic The family has a natural life history of its own on the other hand every person in his lifetime has several different fam lie one for each period of his life

Among the number of social purpo es that the family serves two will be par ticularly mentioned (1) It determines *the forms of behavior that are required* in the fundamental and prominent roles within it and (2) it provides training toward integration into a wide range of social roles and acceptance of ocial re pon ibility Specifically family rela tion hip *controls the quality quantity* and direction of emotional expre sion it regulates and patterns the form and range of opportunities for security pleasure and self realization it develops a sen e of responsibility for the welfare of others it teaches evaluation of a pected danger in a situation it in ten ifie or le ens anxiety and it in fluence the choice of defen es again t it

Obviously to fulfill these purposes tability of the family i important The tability of the family and it members hinges on a delicate pattern of emotional balance and interchange The behavior of each member is affected by every other member The degree of tability in family relation hip is the end product of complex interdependent proce es for it is governed by the interaction of family mem ers in their respective family role One require ment for stability is maintenance of con tinuity of identity Against this are balanced the requirements of capacity to change through receptivity to new experience and learning to achieve further development and to fill new life roles Effective adaptation requires a favorable balance between this pro tection of continuity and accommoda tion to change The homeostasis of behavior—the balance between con tinuity and change the clinging to the old and receptivity to the new—is influenced in turn by the capacity to cope with conflict Operating to prevent a conflict to establish a protective equi *librium or to compen ate for conflictual* effects is the pattern of family role relations called complementarity Failure to find an effective solution for control of conflict leads to adaptive breakdown which engulfs all members of the family

Through faulty functioning the family may become a source of tres or fail in its support of a member already under pressure outside the home When a family becomes di abled and its opera tions impaired its stability is threatened *Usually such impairment in performance* is not total but partial Some compo nents of family functioning maintain their integrity while others are disabled Families exhibiting deterioration may be thought as of progressively failing to carry out their e sential family function Ackerman ha dev ed a system of grad ing familie which expre es quantita tively the extent of their disability

Breakdown in the psychological oper ations of the family group does not occur all at once Initially it may be rela tively localized and may be manifested in impairment of the family s capacity for problem olving and dec ion mak ing In the beginning the di integra tive effects of breakdown may be rela tively ubtle but by d grees they pread progre ively to affect mor and more of the family s ba ic function At this point manifestations of breakdown

disorganization are so unmistakable as to be easily detectable isolation of family members critical barriers to communication conflict and hostility di integration family unity With the e developments the family as a group can no longer fulfill even its minimum functions

During the cour e of deterioration efforts may be exerted to halt or re verse it Families vary in their capac ity to contain those problems for which they cannot find a olution while en deavoring to make some tolerable re ti tution Such compensatory behavior is pos ible only when despite conflict and alienation some family pairs are able to maintain a atisfying pattern of complementarity In one way they may damage one another yet in another they may provide material upport and ati faction of mutual needs

Not to be overlooked is the relation hip between family conflict and psycho logical conflicts within a member This relation hip is a basic influence on both individual and family stability for the tability of the individual per onality is partly dependent upon the stability of the family Here again complemen tarity in family role relations funda mentally influences the course and out come of per onal conflict

Stre s in the family has focal point that are readily recognizable As a group the family develops a major pat tern in its difficulties In ome the major area of stre s centers in the marital relations in other in parent child relations in till others in the truggle to reconcile the requirements of multiple roles or to establi h the po ition of the family in the wider community Stress and conflict emerge when the behavior of a member in one family role fails to complement the needs of the member in the reciprocal role

Methodology—It is difficult to corre late culture or personality with either tre s or somatic illne s unless the refer ence group is also interpreted for mo t influences upon the individual are regi tered through the intervening network of interpersonal relations The family is one of the most influential group Accordingly the individual should be studied not in isolation but within the framework of his ongoing experience and interchange with the family group In that context personality and life histories of individuals may be studied in relation to stre s and somatic illne s

In an examination of the family in its relation to stress and somatic illne s it is clear that all elements mu t be in cluded the individuals the family group and the various interrelation hips In particular this examination should cover the following areas each member s per onality his interactions both within his family group and out side with the wider social unit the in ternal organization of the family it performance of functions which in fluence each member by inculcating both family roles and the social re pon sibility which comes with wider ocial roles and the external adaptation of the family to the surrounding com munity

When a person conceives of a itua tion as di turbing or threatening he reacts with ten ion and anxiety In this circumstance he con iders which of his resources may be mobilized to protect him and to allay his anxiety In order to understand the personalized disturbing element in the ituation and the individual s reaction to it it is necessary to look into the individual s personality conditioning and defen es But the individual is an interacting member of his group hence it is es ential to study him and his life in the context of his group

In a tudy of the family as the related group certain points hould be ob served major areas of tress pre ence of conflict tate of tability or deteri

oration performance of ba ic functions e pecially support of a member who mav have anxiety, and interplay of individual and family group defenses agam t anxiety It is necessary to mea ure the extent of p ychic resources for control of anxiety both in the indi vidual and in the family group and to correlate the defense behavior of the individual with that of the network of clo e relationships since the latter compo ite plays an e sential part in the mobilization of defense against the effects of anxiety Somatic breakdown is related to the success or failure of the e defen e operations In fact it i impre sive to note the apparent cor relation between crises in somatic func tioning and the relea e of acute anxiety l ecau e defen es break down Thus when the individual is studied within the family group it is possible to relate the occurrence of illness to an epi ode of anxiety and to breakdown of de fen es

Ackerman has developed a method of examining the family and has pub li hed a detailed guide for it applica tion* His examination include the following behavior components the relative autonomy of the individual his emotional integration into family group that i the adaptation of hi personality to the required family roles the fit or lack of fit for the ame individual of ignificant familial or extrafamilial role the extent to which the reciprocal role behavior of other family members support or threaten the stability of the individual and the psychological identity and value orientation of the family group and its external adapta tion to the community Data obtained on these points provide the ba i for determining the nature of three inter related ets of processes (1) What goes on inside the individual (2) what goes on between this individual and other significant family members and (3) psycho ocial patterns of the family as a whole

Several reported investigations on ill ness in relation to the family have con centrated on one or another a pect of family life e g the role of cultural values situations of crisi

The Individual His Personality and Psychological Reactions

We now return from the environment to the individual and his susceptibility to both stress and heart di ea e It ha been postulated that certain individuals are more vulnerable to stres of these a certain number appear to be prone to develop coronary di ea e or its cir culatory precursor For two rea on this subject has practical significance (1) the elucidation of factors re pon sible for the development or precipi tation of heart di ease and (2) the ability to predict the probability of the occurrence of heart di ea e and to make early identification of probable victim as a basis of prevention

Vulnerability to stre s and vulner ability to coronary di ea e are two dif ferent characteri tics yet becau e of their possibly significant a ociation they may profitably be tudied either eparately or jointly A person s rela tion to stress exhibit two a pect (1) his ensitivity to tre s i e the appro priatene s frequency and inten ity with which a person conceives of situa tions as di turbing and (2) the nature of his reaction to that tre It i po ible that a particular type of reac tion to tress may be one of the factor influencing the occurrence or cour e of heart disea e Such a equence would explain in part any vulneral ility to the cardiac complex

Is there a particular per onality type a ociated with development of heart

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A kerman N W *Life Stress and Bodily* D sea e Character Structure in Hyperten i e I son R s P d l A Nerv & Ment Di 9 900 9 8 Balt m re M l Williams & Wil ki 1950

di ease? What are the characteri tics of such an individual? These seemingly simple questions open a very large and complex area The meaning of per onality itself has been an elusive ub ject Allport has compiled more than 55 definitions of personality which have been propo ed at one time or another Since the method of distinguishing per onality types depends upon conception of the nature of personality it is theo retically po sible to have a different method for every definition

Actually four tudies have reported on personality type and heart disease or ome a sociated sign such as hyper tension U ually these tudies were conducted after signs had developed Accordingly the significance of the re ported observations has been questioned Did the observed per onality pattern precede or follow the occurrence of coronary disease or hypertension? Or did the same factor or et of factors that produced heart di ea e also bring about the per onality change? It may be said at this point that investigators believe that the personality structure has been laid down long before the appearance of heart di ease

It will be recalled that Wolff and Hinkle found that whether a situation is capable of inciting stress in a person depends upon his perception of the ituation its meaning and its value for him This point of view is in harmony with the possible vulnerability of an individual to stress

After reviewing those ob ervations and conclusions which bear upon the topic of vulnerability and characte ristics of the vulnerable Dr Hinkle propo ed a type of procedure to obtain further knowledge People differ in their su ceptibility to illness regardless of its nature Tho e who became ill most frequently were found to be more likely to develop both more varied illne es and more evere illnesses than tho e who became ill le s frequently All type of illness seemed to occur ome what more frequently during period when the individual was having diffi culty in adapting to the total configura tion of his life It is to be expected that a man s adaptive reaction pattern will exhibit a variety of alteration depending upon his own constitution previous conditioning and the circum tances he encounters Con equently it ll understandable that he would develop a variety of illnesses

It is rea onable to assume that cardio vascular di ea e might be among the di orders arising out of man s inter relation with his environment As he goes through life man might have an adaptive reaction pattern that i re flected in the function of his cardio va cular system and if continued over a sufficient period of time this pattern might produce disease Thus men de veloping cardiac pathology will not nec e sarily be different from those con tracting other illnesses except po sibly in one or two characteristics of the specific adaptive reaction pattern rele vant to the cardiovascular system

Hinkle pointed to the need to find out more about the characteristic both physiological and psychological of per sons with cardiac di order and their reactions to ituations More specifically he proposed trying to identify (1) the nature of the challenge in the situation (2) any peculiarity in the evaluation and (3) the nature of the cardiovascular reaction pattern He pointed out the desirability of taking general hypo the e developed on evidence from the laboratory out into the field Unfortu nately in atherosclerosis and heart di ea e the laboratory evidence on which hypothese may be built is quite limited Possibly the best hypotheses at hand were derived from limited laboratory ob ervations on persons placed in rela tively acute situations to which they responded In these tudies mea ure ments were made over a rather hort

period of time on a limited number of variables

One such hypothesis would be In hort term experiments persons may be subjected to situations which are de igned to threaten them As part of their reaction some of them will de velop elevation of blood pressure Some persons perceiving their life situations a threatening to them al o exhibit an adaptative reaction which includes an increase in peripheral resistance with elevation of their blood pre sure If thi adaptative reaction were carried on over a long period of time it might ultimately produce hyperten ive cardio va cular di ease

How does one identify persons who are prone to this type of reaction? A proportion of the people who react in thi way seem to have a ingular mental pattern which makes them easily threat ened by a variety of circumstances They react to this situation with an aggressive feeling which they have dif ficulty in expres ing

Not all of these persons necessarily have anything abnormal about their cardiovascular apparatus Many people in the population who have this person ality trait do not have hypertension On the other hand a ignificant number of hyperten ives do not have this trait Nevertheless it is probable that this trait occurs more frequently in hyper ten ive

One way to test thi hypothesis would be to study cardiac morbidity rates in populations which differ in their conception of certain threatening circum tance i e whether they see them elves a threatened For this it is necessary to turn to the anthropologi t It is a rea onable a umption that certain o cieties facilitate in their members ready expre ion of the aggres ive re pon e elicited by such threat while other so cieties hinder it Some people are in a ituation in which their treatment by ociety i likely to arou e in them a great deal of ho tile resi tance which they cannot expre s because that would only make the ituation wor e

Another hypothesis may be cited When certain people are faced in life with situations that they regard as threatening the biologic re ponse will include a ignificant rise in the blood cholesterol If this metabolic reaction pattern is u tained over a period of time it is conceivable that it facilitates the development of athero clero is

In a certain number of people thi type of adaptative reaction is as ociated with mobilization Thi rai es the po ibility that it is the triving member of our society who are particularly u ceptible tho e who get up earlier work harder and longer and keep going all the time

To test this thesis again we turn to the anthropologists to identify ocietie in which this pattern seem to be preva lent and other ocieties in which it i not

From studies over a number of years of the personality characteri tic of hyperten ive patient Ackerman ha developed a hypothesis In evaluating the character structure of these patient he ha placed pecial empha is on their defen e behavior and role adaptation They exhibit he has noted a pyra miding series of specific hock reaction in the per onality representing the re pon es to experiences conveying real or symbolic threat In these reaction the proce es for control of emotion are acutely overwhelmed and the adaptive functions of the personality undergo im pairment or breakdown Specifically the defen e mechani m of repre ion proves inadequate auxiliary defen es which are then mobilized al o are in uf ficient With this paraly is of the adap tive proce se a tate of temporary emotional disorganization i induced There i a loss of balance in the inte grative functions of the personality at all level This inadequacy i reflected in

the failure to maintain a characteri tic ocial role which is significant in the preservation of ecurity in interpersonal relations It is assumed that the poten tiality for this particular form of shock reaction depends on the specific pattern of emotional predispo ition conditioned by the vici itudes of experiences during the formative tages of personality Thus there is believed to be a basic factor of vulnerability in the personality which long antedates the emergence of overt symptoms of hyperten ion

The generalized impairment of adap tive capacities in this shock reaction is tran itory The lo s of emotional control while profound i brief equilibrium is quickly re tored After a series of such critical epi odes precipitated by trau matic life experiences which symbol ically pell a danger the pre ence of hypertension is often revealed Its on et is associated with a pyramiding series of pecific hock reactions in the per onality In the later tage fixation of the di tortions of adaptive function of the per onality is een involving in crea ing rigidity of the psychophysical mecham m of the personality The com ponent of conflict which is primarily re lated to the hypertensive reaction is that which occurs between the person and the environment rather than the per on s conflict with self In um it is believed that a preexisting vulnerability in per onality plus the reactions to trau matic life experience produce the con dition in which blood pressure is elevated at fir t reversibly later perma nently

From his study of hyperten ive per son Ackerman has gained impres ions of their per onality Their behavior ug ge t that they would like to act out and to behave like psychopaths but do not dare

Acting out ignifies a situation in which a per on is experiencing a con flict which cau e him distres and which he cannot cope with in a rational and appropriate way Thus his manner of re olving this conflict is likely to get him into trouble because his action does not fit the social situation From that action unpleasant consequences may en sue but for the moment the individual has ucceeded in relieving the exces ive tension and has established an equili brium for his internal life

The behavior of a psychopathic per sonality illu trates acting out He i a highly egocentric person who is anti ocial gets into trouble with his ur rounding ocial group ■ again t everything l id down by prescribed o cial behavior defies tradition and gets into trouble with the law The psycho path acts as if he were more powerful than the forces of his environment He acts en ele sly as if he had some magi cal power to make him elf tronger than anyone else in his social group

In characterizing the personality of the hypertensive patient as a would be psychopath Ackerman stated that such a per on is motivated in phantasy by a desire to live like a psychopath But he doe not dare The fear of retaliation is overwhelming So he does not have the ability to master the environment with hostile aggressive power On the other hand he is not able to accept and execute a role of submission to and de pendence on the environment Obviou ly the two roles are incongruous and irre concilable That is his dilemma

Hence he acts in It is no surprise to ob erve reactions in the inner organ y tem When tension cannot be relea ed in the voluntary muscles it may flow over into the sympathetic and parasym pathetic systems It i however an in appropriate failing type of mobilization of defen ■ against tension

Ackerman has explained the psycho logical proce es underlying this be havior One prominent manifestation in a hypertensive person is the overten e conflict experienced in the effort to con trol aggres ive impul es and the ten

dency to suppress the translation of such impul es into action Suppression occurs because the usual defenses are un uita*ble and defective* Attempts to cope with impul es through repression are un uc cessful and auxiliary defen es also are inadequate It is not clear that thi pattern of defective repres ion i pecific for hypertension it may prove to be a common pattern in a variety of psycho o matic disorders Con cious suppression of emotion represents the final defense again t the threat of los of control If the ba ic impulses were to break through the control mechani ms and be dis charged into action it i likely that the *resulting behavior would* be either psy chopathic or psychotic When p ycho o matic phenomena appear instead it is believed that they represent a substitute for a break through of emotional control with direct translation of impul e into action

The component of conflict which is critical in the hypertensive phenome non and possibly in other psychosomatic disorders as well i that which takes place largely at the level of translation of conscious or precon cious emotional experience into action i e the level at which the patient struggles with ome degree of conscious ne s to act against the presumed dangers of the environ ment The patient s reaction reflects a strenuous effort to control or even ac tively reshape the environment whether at the level of reality or at the level of omnipotent mastery The implied urge is to mobilize magic power in order to coerce significant persons into a pro tective and upportive role It therefore seems that the externalized rather than the internalized component of conflict is *pecific and* crucial for hyperten ives

In the proces of adaptation ocial role may repre ent either a po itive ex pre ion of indivi*duality* that i role and per onality may coincide or a nega tive function of defense In the latter case the effort to execute a particular social role may exact an exces ive price in the terms of conflict and anxiety within the individual Or the inner con flict may be such as to damage or ac tually prevent the execution of a given ocial role

The relative success or failure of adap tation in the context of a given role is partly the re ult of coincidence or con flict between a particular character dis position and a particular group environ ment with its status and role

For the e rea ons the relations be tween personality and environment have much significance in the development of hyperten ion It would appear that the link between emotional reactivity and the hyperten ive response i e psy chological pecificity is to be sought, not in the content of conflicting drive nor in the total per onality configura tion but rather in the pecific pattern of defect of the mechani m of control *of emotion in a situation of undue tre* between the person and the environment All that has been said sugge ts a focus of interest on the structure of the ocial environment and on the ego regulatory mechanisms of personality in hyperten ive e pecially the preci defen es which they employ against impulse di charge and anxiety Accordingly any p ychological specificity is to be ought in tho e mechani ms of the hypertensive per on which integrate emotion and con trol tran lation of impul into action in the performance of a ocial role In hort the emphasis is on role adaptation and defense behavior

It thus becomes nece ary to a certain (1) the particular ego integration patterns and defen employed in a given role (2) the degree of adaptive efficacy or failure (3) the manner in which such defen es are periodically overwhelmed (4) what forms of com pen atory defen e are erected in the pha e of recuperation following a tem porary break through of emotional con trol

To obtain this information in testing the validity of the hypothesis the usual psychoanalytic approach is inadequate It does not provide a sufficiently accurate cross section appreciation of total character in particular those patterns of character integration that in a given time and given environment are projected into a given social role Actually psychoanalysis is not oriented toward examining the social self Rather it has tended to emphasize a denuding by the patient of the social layers of his identity in order to gain access to the unconscious and biologically conditioned drives Thus it keeps in abeyance the very ego integration that would be a principal object of study in hypertensive persons

Ackerman has devised a guide for the evaluation of total personality function in the context of the present time and the present life situation It stresses pattern of ego integration oriented to the maintenance of a given social role or role in a given environment He emphasize that the personality should not be disassociated from the environment Rather the two should be treated as a functional entity The picture of the patients personality should be unified and dynamic and his functional relation with his environment should be preserved Ackerman suggests that this mode of analysis might profitably be applied to a larger group of hypertensives

Professor Carney Landis offered still another approach to determining the characteristics of person who develop cardiac disease He pointed out that most scientific discoveries have resulted from someones asking the right question For effective results from direct interrogation a set of relevant questions must be designed for the occasion If he were to undertake such a type of study on cardiac disease he would first obtain *from* a number of cardiologist what they thought were the relevant questions Then he would design the interview

The biggest obstacle to such an inquiry by direct questioning is the scarcity of suitable interviewers It should be strongly stated that interviewing cannot be turned over to unskillful and untrained persons It takes a long time to find and train competent interviewers

In order to discover the characteristics of persons vulnerable to heart disease Professor Landis would question two groups (1) persons with undoubted hypertension and (2) those who had had a coronary attack He would ask them pertinent question to find what their life experience psychological problems and social relationships have been

To the protest that many coronary patients could not or would not submit to an interview Professor Landis maintained that any question can be asked if it is asked in the right way and under the proper circumstances and it will be answered

He recommended that the application of any tests should come only after completion of the survey by interview never before Only after the relevance of questions in the interview has been confirmed is it possible to prepare tests for the investigator must apply tests that are relevant to the intended use In his opinion there is no available psychological test which has any relevance and therefore any primary value in cardiovascular disease On these ground he would not apply the Army Alpha Rohrschach or Thematic Apperception Tests Nevertheless he thinks that after the survey by interview has indicated the pertinent questions it should be possible to design tests with the requisite relevancy for cardiovascular disease

Worth noting is Professor Landis estimate that to properly conduct a study by direct questioning would require 15 years

Genetics

At the outset of consideration of genetics in relation to heart disease two

points hould be kept clearly and em phatically in mind In a en e they are the present day doctrines of genetics One principle is that what is inherited for the most part is a potentiality not an inevitability . Whether this poten tiality develops into an actuality depend primarily upon environmental circum stances Thus genes do not exert an ab olute control but determine potential development in particular environmental situations The second principle which is really a corollary of the first recog nizes that gene and environment are interrelated that an interlocking net work of hereditary and environmental influences determine the outcome

Conceivably genetics may influence in several different ways the develop ment of coronary di ea e it may act tructurally or functionally at various stage of pathogenesis This po sibility raises a number of questions for investi gation In general the numerous rela tions and que tions concerning them may be grouped in three major cate gorie

The paramount question goes right to the crux of the matter Is there a hereditary predi po ition to coronary di ea e? To answer this question re quires a direct over all approach which does not nece arily cast any light on the mode of relationship But its an wer would provide fundamental information which would have practical application in the prevention of heart di ease

A ide from its value per se the an wer might dovetail with knowledge of pe cific points in the hypothesis of the equence in pathogenesi Determination of whether there is a vulnerability to cardiac di ea e for which genetics has at l a t a hare of the respon ibility might complement exi ting partial evi dence on the equence of event in pathogen i in consequence to that ex tent it might place the hypothesi and its parts on a more ul tantial footing Out of the group of person with an adaptive reaction leading to frequent illness from a variety of di ea es why do only ome person contract heart di ea e? What is the basi of this selec tivity? To answer this question it is important to find out whether certain persons inherit a potentiality for de veloping coronary di ea e Surely it would al o stimulate a number of inves tigations on pecific point For the over all approach available methods such as study of hereditary lines or twins are well known

The econd large question concerns the po sible di tinctiveness of person who will develop coronary disease and the genetic transmis ion of this quality Can uch individual be characterized in a prototype? Are there recognizably di tinctive characteristics associated with a per on who tend to develop coronary di order? Are the e features tran mis ible? Demon tration of an a ociation between a distinctive type of person and hi vulnerability to heart disea e rai es the que tion whether his characteri tics have any hereditary ba is

There have been a numl er of efforts to type per on who develop or have coronary di ea e for valid typing would be extremely u eful It would provide an index for identifying potential coro nary victim so that preventive mea ures might be in tituted Furthermore al though typical characteri tics might not explain the pathogenesis of heart di ea e they might furni h a clue to the ignificant features of the proce If the characteristics were found to be un der genetic influence the u efulnes of typing would be enhanced on l oth score

For present purpo es it i de ira l e to know whether well defined ea ily recognizable characteri tics validly ig nificant and pecific for coronary disea e are available for u e in genetic tudies Attempts have been directed at two ba es of di tingui hing person body type and personality Gertler and White have re

ported that coronary di ease occurs more frequently in persons with endomorphic me omorph body build Technics of physical measurements and a number of systems of classification of body type were developed long ago The selection of significant physical measurements and the validity of the systems of clas i fication have been the objects of critical comment and difference of opinion

Four tudies have been conducted on the per onality type as ociated with per sons having hyperten ion Briefly tated the pre ent attitude is that it is less promising and less profitable to establish per onality type associated with coro nary di order than to investigate the p ychological reactions especially role adaptation and defense behavior of per sons who develop hypertension and coronary disease

The third area of investigation by genetics has to do with the various pathological changes in heart disea e sugge ted reputed or demon trated to be under genetic influence They may be arranged in four groups psychologi cal physiological biochemic al and his tological At one time or another eight different changes have been specula tively a ociated with genetic influence It is to be borne in mind that for the mo t part the relation of these changes to genetics is at present a postulation These changes are shown in the follow ing tabulation

P-ycholo ical	Bioch mical
Role adaptation and d fen e behavior	Hypercholesteremia L poprotein Blood coagulat on
Phy iol ical	**Hi tolo_i al**
Vascular hyperactivity Tran ient hyper ten on and tachy ardia	Arterial wall width Defect at unction of intima and med a

From examination of this tabulation it is obvious that genetics may be related to three level of cardiac disease ac cording to the nature of the pathology structural functional and metabolic Hence genetic methods must be applied in conjunction with morphological phys iological and biochemical technics

Only four changes were considered in detail by the group adaptive re action a lesion at the junction of the intima and media in the coronary ar tery lipoprotein and blood coagula tion

Why ome persons react to tre s with illnes but why only certain of the e de velop cardiova cular disea es are ques tions u ually explained by attributing this selectivity in part at least to genetic influences These que tion make perti nent the inve tigation of the po ible re lation hip of two separate phenomena to genetics One of the phenomena—namely genetic influence in the selection of the heart a the vulnerable point—has already been di cus ed

Now the non pecific adaptive reaction comes under con ideration Here the ob jective is to ascertain whether the adap tive reaction and its apparent re ponsi bility for vulnerability to illness as indicated by the frequency with which it is a_ociated with illness in particular individual is determined at lea t in part by genetic processes For present purpo es vulnerability to illness is of intere t only in so far as it indicates the type of adaptive reaction that is responsible It i assumed that this re action could lead to cardiovascular disea es or any of a number of others depending on different factor As uch it may be regarded presumptively as one stage in the pathogenesis of cardiovas cular disease If this type of adaptive re action is conducive nonspecifically to heart di ea e it is important to ascertain whether this reaction has a genetic ba_is i e whether certain persons inherit a potentiality for developing it But to es tabli h a genetic relation to any charac teristic one mu t have a reliable means of identifying that distinctive feature At pre ent there is no quick and sure

means of accomplishing this identification Hence application of a genetic approach awaits perfection of an identifying method

Next to be considered were the processes relevant to the development of atherosclerosis and thrombosis and conceivably affected by genetic influence In describing the formation of the atherosclerotic plaque Dr Wilkinson pointed out that two theories have been proposed to explain the origin of the early deposit One postulation is that there are always circulating in the blood tiny thrombi which may attach themselves to the vessel wall one does attach itself and starts to organize during the process of organization fatty infiltration and calcification occur The second postulation about the process of atherogenesis called the infiltration theory has wider acceptance on the continent According to this theory there is a constant flow of fatty particles from the inside to the outside of the vessel But for some reason in atherogenesis infiltration builds up at the junction of the intima and media of the coronary artery and lipid material collects to constitute a formation In composition this material at first closely resembles the circulating lipids of the blood i e the lipoproteins As the lipid infiltration ages its composition changes relatively more cholesterol and less of the other lipid are present If this infiltration progresses it becomes a yellow or lipid plaque As this lipid plaque ages scarring and calcification may occur until very little lipid material is left The resulting pearly plaque is composed of fibrous tissue and calcium

Atherosclerosis is widely prevalent most adults are found to exhibit it In the two sexes there is probably no difference in the total amount but there is a difference in distribution In the male the coronary artery is more frequently involved in the female it is seldom affected until after the menopause It is postulated that atherogenesis in the coronary artery is associated with an inherent defect at the junction of the intima and media and that this defect is an inherited characteristic

Despite the widespread prevalence of atherosclerosis it is only when a complication such as the formation of a thrombus on the eroded surface of the plaque sets in that clinical disease may be said to have occurred For this reason the amount of atherosclerosis is not so important as the chance distribution of it

Various factors influence atherogenesis The rate and manner of formation of the plaque is affected by primary and secondary factors Age and sex are primary factors With age there is a tendency toward increased atherogenesis Quite apart from the effect due to hormonal differences are the anatomical effects of sex on atherogenesis At birth differences may be distinguished between male and female coronary arteries both in thickness and in anatomical configuration in the heart These primary factors favoring the female would probably account for from 2 to 3 per cent of the difference in death rate for coronary disease between males and females if there were no secondary factors

Among the secondary factors affecting atherogenesis may be mentioned hypertension diabetes renal disease hypothyroidism hyperlipemia and hypercholesteremia Hypertension is probably the most important factor in the list Of the remaining factors hyperlipemia is of special note because of its relation to the clinical disorders In effect those metabolic diseases that increase the rate of atherogenesis remove the female sex protection For example female diabetics at any age are just as likely as nondiabetic males to have atherosclerosis The one common denominator in the metabolic conditions that remove the female sex protection is a secondary hyperlipemia

Genetically determined hyperlipemia appears to be indistinguishable from secondary hyperlipemia With the hope of comparing within family groups the effect of hyperlipemia nine genetic types have been postulated In setting up genetic studies it is important to *find the carrier state* Hyperlipemia is noticeable in the homozygous It may also be observable in the heterozygous individual by the time he is 30 Dr Wilkinson emphasized that if every person between the ages of 25 and 35 merely had his blood inspected and his *diet adjusted if he were found to have* hyperlipemia from 3 to 10 per cent of potentially fatal coronary diseases could be prevented When all the possible secondary factors in the development of the atherosclerotic heart are studied it may be that some of them will be found to be just as important as *hyperlipemia* or even more so

Medical genetics is in the midst of an extraordinarily active and fertile period largely the outcome of investigations into the biochemical backgrounds of disease Accordingly Dr Block presented *the biochemical* approach to genetics with special consideration of lipoprotein patterns and heart disease Before indicating promising lines of investigation he reviewed the biochemistry transport and intermediary metabolism of lipoprotein

Total lipid in the blood comprise neutral fat cholesterol cholesterol esters and phospholipid In the blood stream these lipids are carried in combination with protein These lipoproteins make up from 12 to 15 per cent of the total protein in normal human plasma Serum *protein itself* is composed of two heterogeneous groups of proteins—albumins and globulins—but it may be further fractionated Electrophoretic analysis of serum protein yields a diagram containing five to *ten protein boundaries* depending on the type of fractionation Each boundary is indicative of a separate group of proteins The first boundary represents albumin the remaining boundaries globulins In order the latter are designated alpha 1 alpha 2 beta and gamma About 75 per cent of the serum lipids are carried in combination with the protein in the beta globulin *fraction Only a small proportion of* lipid is carried with the alpha protein fraction

How lipid and protein are combined and how tightly they are bound are not exactly known It has been suggested although not proved that there is *a core of protein with active groups* of amino acids on its surface This core holds these molecules together through attractive forces between nonpolar peptide residues such as leucine and phenylalanine and the fatty acid of the lipid moiety

What happens to lipoprotein in the blood stream in the utilization of lipids? It has been postulated that there is a normal level of lipoprotein in the blood That level is exceeded when lipoprotein is unable to take up more neutral fat that point is the high level of lipoprotein *fat combination Then from tissue* an enzyme or clearing factor lipoprotein lipase is released When it comes into contact with the lipoprotein it splits off the neutral fat fraction in glycerol and fatty acid thereby regenerating the protein to be available to pick up more lipids

In the biochemical approach to the study of genetic influence in any disease it is necessary to select a specific characteristic to be investigated In the present instance it may be a lipid constituent of the blood such as neutral fat Whatever it is its validity and significance is usually established through its occurrence in patients with clinical signs of a particular disease Also blocks and aberrations may occur in several ways *and in various stages in the metabolism* of a substance For one thing the metabolic block may be found to be a so

ciated with an enzymatic aberration Whatever the detectable abnormality the pecific characteristic is traced genetically Sometimes the tracing is best undertaken in genetically isolated groups

Block pointed out that a metabolic abnormality may be found in either of two stages biochemically manifest or latent In some persons it may be readily detected by an appropriate biochemical method in others it is in a so-called carrier state which may be revealed only after special measure For full and complete application of genetic principles detection of the carrier or susceptibility state is highly important Perhaps one way to reveal this state is to impose an appropriate stress or overload upon the subject Two examples illustrate the point When a family is being studied for occurrence of phenylketonuria the abnormality will be found regularly in the urine of some members but will not be detected in others However Jervis has indicated that the administration of phenylalanine to patients with this disorder may lead to an abnormal phenylalanine tolerance curve Another means of detecting early evidences of diseases which develop late in life is a technic devised by Conn and Fajans which utilizes stress for the recognition of susceptibility to diabetes In both examples the susceptibility which would otherwise go unnoted is detected by a form of stress Emphasized was the possible usefulness of detection of the carrier state in studies of heart disease Practically detection of the carrier state opens the possibility of delaying or preventing the manifest disease

Block proposed three studies in a biochemical genetic approach to heart disease In one the objective would be to measure the clearing ability of the sera of persons with hyperlipemia Normally the enzyme lipoprotein lipase cannot be detected in the blood But if heparin is injected into the subject his blood shows within five minutes a rapid increase in its ability to clear neutral fat i e turbidity and hyperlipemia disappear From these and other observations it has been concluded that heparin produces a profound alteration in the lipoprotein pattern If this lipemia clearing test were applied to patients with hyperlipemia it might be possible to detect whether they have a normal response to heparin with liberation of the tissue enzyme which is instrumental in the utilization of neutral fat or whether they have a disturbance in the release of the clearing enzyme

As a second study Block suggested that the level of lipoprotein fractions in the blood of persons in family groups should be determined and the results genetically analyzed There is some evidence to indicate that a carrier state may exist in hyperlipemic persons which is detected in the alpha lipoprotein fraction From studies on a large family through several generations Adlersberg has reported an aberration in the alpha lipoprotein

Third Block recommended that detection of the carrier state by biochemical method be applied to genetically isolated groups It is here that the procedure has its greatest effectiveness As an example he described its application in the study of primary systemic amyloidosis in a genetic isolate Upon ultracentrifugal analysis of serum lipoprotein from 66 subjects 29 showed an abnormal pattern in the alpha 2 globulin region which corresponded approximately to the position of an atypical peak in electrophoretic diagrams Although biochemical analysis of lipoprotein from individuals with clinical signs was important if only to establish the clinical significance of the results its greatest usefulness was in detecting the subclinical the so-called carrier state For these reasons Block recommended studies of the relevant biochemical char-

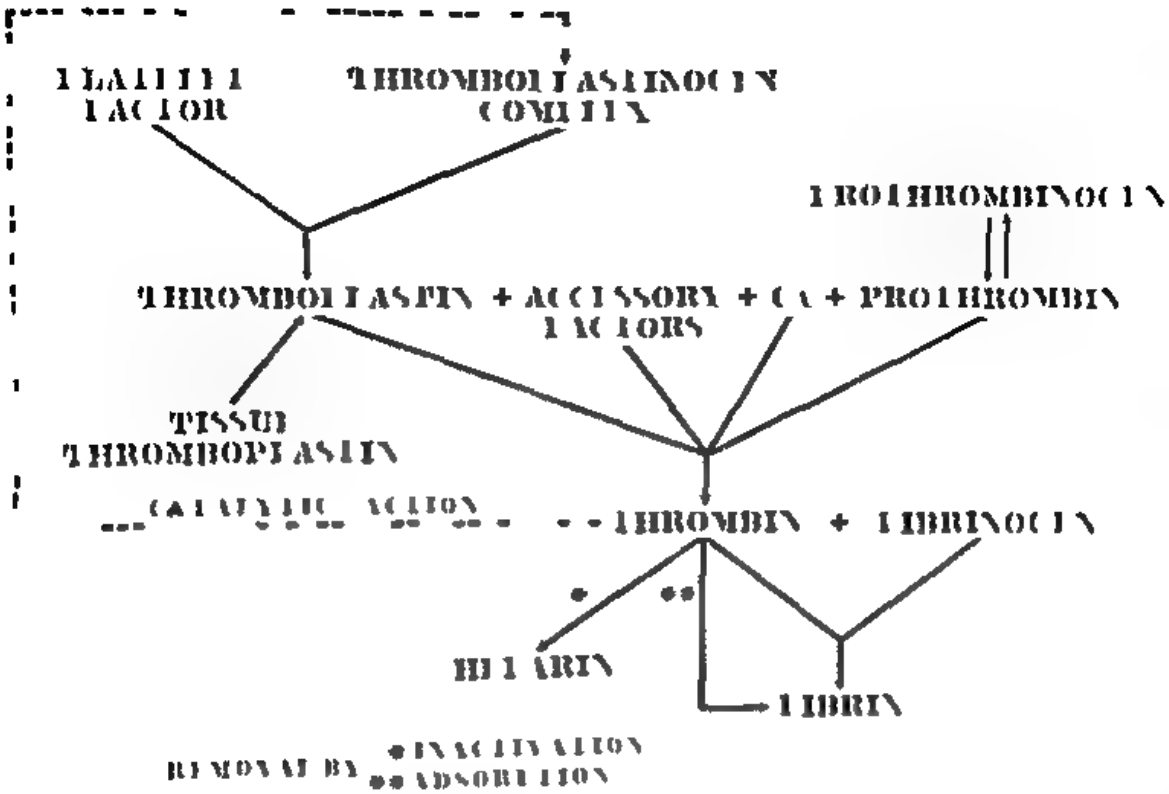


Figure 1—Schema of Blood Coagulation

acteristics of heart disease in genetically related groups

One of the most significant developments in the pathogenesis of coronary disease is the formation of a thrombus which may lead to occlusion This possibility—an actuality all too frequently—raises several questions whether the blood of some persons is in a hypercoagulable state whether that state is measurable whether it is attributable to an abnormality in the blood and whether it has a genetic association In approaching the subject Dr Quick presented such evidence as is available Then as an aid to understanding both his explanation of his observations and the rationale of his subsequent opinions he reviewed hemostasis the process of blood coagulation and the probable events in the formation of a thrombus

In an attempt to determine whether a thromboplastic tendency could be demonstrated Quick conducted a battery of tests on the patient with thrombophlebitis The tests revealed no real abnormalities that would indicate a thromboplastic tendency Unfortunately most available tests were not designed to detect coagulability but the opposite hemorrhagic tendency For example in hemophilia the clotting abnormality can be attributed to the lack of a specific factor thromboplastinogen (Factor VIII antihemophilic globulin) But available methods useful in the study of bleeding tendency do not provide such reliable and complete information on hypercoagulability Because of their limitations when applied to coagulability the results yielded by these methods are open to question In Quick's opinion hypercoagulability is measurable neither by the clotting time nor by any other test routinely used in the laboratory

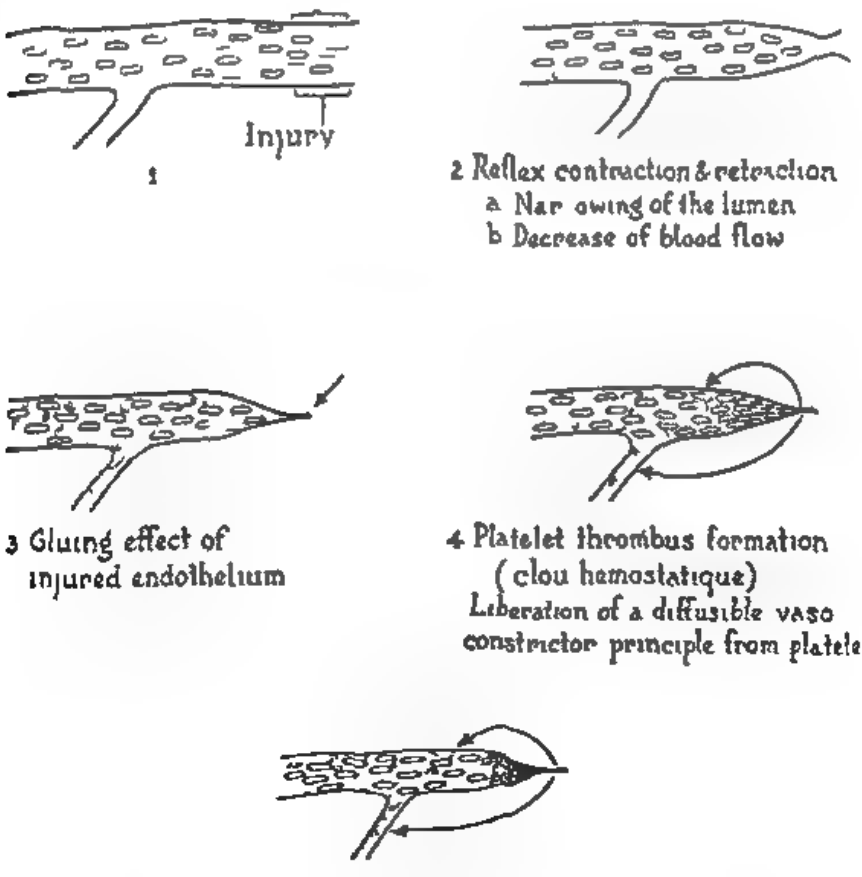
In view of the technical limitations Quick turned to a different approach In raising and answering for himself the question what is hypercoagulability he reasoned that essentially it must involve a greater amount or an increased rate of formation or reaction of throm

bin for after all it is thrombin that converts fibrinogen into fibrin in the formation of a clot Avoiding the more difficult and uncertain course of search ing for ways to rai e the thrombin level by influencing factors that control its formation he went directly to the ex perimental production of a clot by in jection of thrombin When thrombin in high concentration was injected rapidly intrava cular clotting throughout the vascular system ensued But such large amounts of thrombin were necessary that obviously the experimental pro cedure was not comparable to the natu ral occurrence of any hypercoagulable tate Then too the clotting o far ex ceeded the extent which might be presumed to occur from a natural hyper coagulable tate that it did not repre ent an analog

I ut when thrombin was injected at a slow constant rate re ults oppo ite from what might be expected were ob tained Instead of the clotting time being hortened it was prolonged One of the reasons for this seemingly paradoxical reaction is that thrombopla tinogen drops to a very low concentration The level of Factor V is al o reduced What i actually produced i a hypocoagul able state which acts as a natural pro tector mechani m preventing the build ing up of a hypercoagulable state

F gure 2

HEMOSTASIS



It hould le emphasized that it m thrombin which is the all important sub tance in coagulation There are two ways in which it is formed (Figure 1) In one it is produced in the blood per se i e blood completely i olated from tis ue This process requires a complex reaction a platelet factor and a pla ma factor the thromboplastinogen complex form thromboplastin this then reacts with prothrombin acce sory factor and calcium to produce thrombin In a test tube it takes at least from five to eight minutes for that reaction to occur The slowness of the reaction rate makes it mo t unlikely that the body develops a hypercoagulable state by thi route

Quite different is the formation of thrombin from another ource tis ue thromboplastin and by another route Ti ue thromboplastin does not have to be manufactured during the clotting reaction It is widely di tributed in the tis ue When it comes into contact with other factors in the clotting sys tem there is rapid clotting in 12 econd It is ti ue thromboplastin that could be the ource of hypercoag ulability

The first tep in arrest of bleeding i e hemo ta is is vascular con triction (Figure 2) It is a factor in intra vascular formation of a thrombus But the thrombus doe not form in the blood stream in tead it has its origin at the site of an injury to the vascular wall (Figure 3) This clot get its tart from tissue thromboplastin which leaks out the thrombus form rapidly be cau e of the quick action of ti ue thromboplastin Then the thrombus can organize especially if the blood tream is fa t or the clot may attract platelet undergo contraction and extrude erum The erum contributes to further throm bosis with a new clot Provided it is not swept away by the circulation it is superimpo ed on the original throm bu A a result there may le ucces ive growth of new thrombi

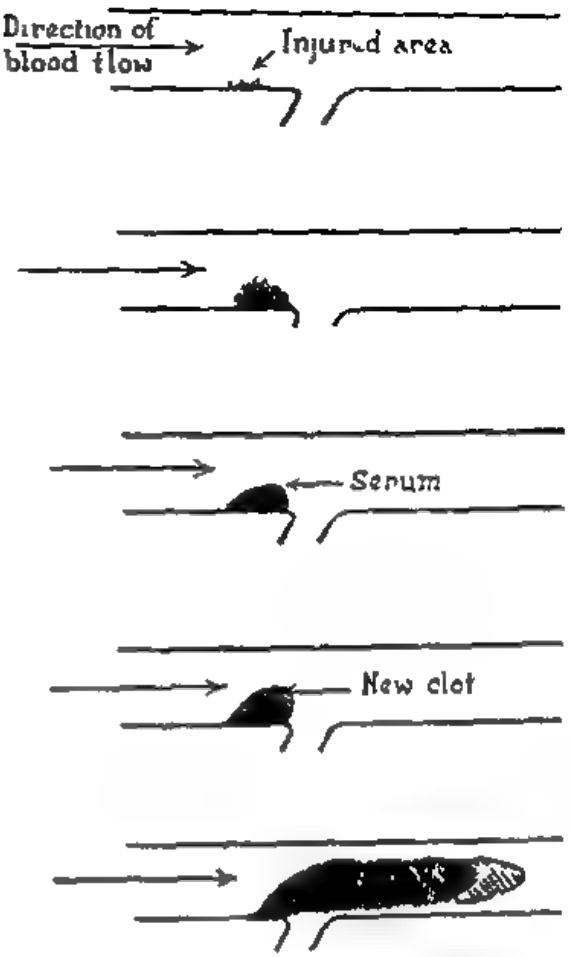


Figure 3—Probable Events in the Forma tio i of ti e Thrombo i

It is important to reiterate that the clot which is a sumed to play an im portant role in heart disea e does not originate from the blood it elf but from the vessel wall It is then coordi nated with the clotting factor Con sequently in Quick s opinion little knowledge concerning thrombo i is to l e gained by study of the blood for coagulation changes Certainly the re ported re ult from studies on the in fluence of lipid on clotting are open to question Since the clot originates in the vessel wall it i there that the search hould be directed in studying coronary thrombo i

Heredity plays a more important role in hemorrhagic di ea e than in any other group of di orders Perhaps it may al o exert an influence over throm bo i But the chance are rather re

mote of finding blood changes indicative of a hypercoagulable state that may be relevant to coronary thrombosis and possibly attractive for genetic analysis. Focusing on the vessel wall seems more promising.

Dr. Jarvik discussed the possible relationship of genetic influence to heart disease at various stages in the hypothesized sequence of its production. Conceivably there may be genetic relationships with both the general and specific aspects of the process.

From the studies of Wolff and Hinkle it has been concluded that when persons have illness associated with an adaptive reaction to disturbing situation they may develop any of a variety of diseases including cardiovascular disease. In a sense they may be regarded as being susceptible to many kinds of disease. These persons may have a generalized constitutional weakness. From this conclusion it may be further inferred that all are capable of developing atherosclerosis provided that they live long enough and are exposed to appropriate environmental influences. In relationship to general constitutional weakness Dr. Jarvik likened atherosclerosis to tuberculosis. With sufficient exposure everyone can contract tuberculosis. Yet there appears to be a genetically determined variation in resistance to this disease, some people succumbing more easily than others. The same relationship might hold for heart disease.

On the other hand, genetics may be more specifically related to the production of heart disease. Not all persons do develop atherosclerosis. Many people die at 80 or 90 with no evidence of it. Only some persons have the capacity. Atherosclerosis can be developed only by those who have the potentiality presumably on a genetic basis. As in schizophrenia so in heart disease only those who have the proper genes contract it.

That both the constitutional and specific processes have a genetic relationship is possible, indeed probable. Conceivably all persons may have a potentiality for developing certain types of cardiovascular disease whereas only those persons with a specific combination of genes succumb to other types. Perhaps the psychological reaction pattern of certain people is based on a particular combination of genes which may be associated with a type of physiological activity that produces hypertension. It would be important to determine these points because at present there is no genetic evidence for them.

To stress genetic influence may be related in two ways. (1) Genetic effects may be largely responsible for the situation creating stress. (2) genetic influence may affect the individual sensitivity and reaction to stress. Situations creating stress may exist in certain families because genetic factors have contributed to the production of other diseases. In families with mentally defective members or schizophrenics the group is exposed to a greater degree of stress than is usual. It would be informative to determine the incidence of heart disease in families experiencing this additional stress. A study is now being conducted to find out whether the stress created by such a disabling condition as deafness which is in part genetically determined increases the incidence of schizophrenia in the family.

In the search to ascertain whether the various pathological changes in heart disease have a genetic relationship the avoidance of one particular pitfall should be emphasized. Any disorder that is genetically determined has its counterpart on an environmental basis. The environmentally produced disorder which is called a phenocopy mimics the genetically determined form so closely that the manifestations of the two types are indistinguishable.

Methodology.—*In order to answer* questions concerning the bearing of

genetic influences on heart disease both twin and family studies are needed One of the mo t important objectives hould be to ascertain whether genetics exerts an influence on cardiovascular di ea e and if so whether it would be po ible to identify individuals who are particularly vulnerable to the disorder Then it would be u eful to apply studies of twins in a somewhat different way than is usually done Once vulnerable individuals can be identified it would be profitable to search in the environment for significant variables that affect them and bring them down with cardio va cular disea e Becau e it would be rea onably certain that such a group has the potentiality of developing the di ease it would be the only group in which the influences of environmental factors could be so readily studied

Originally twin studies were designed to reveal the importance of genetic factors by comparing the rates of preva lence of a di ease in twins and iblings Ju t as valuable if not more so would be twin studies in conjunction with experimental exploration of environmental factors When u ed in conjunction with the application of therapeutic method twin tudies could be very u eful in investigating physiological and biochemical variables

In exploring the environment for rele vant and significant variables it is helpful to follow clues By the same token it is more important to ask the right question than to test a random erie of correlations Studies already under way have indicated a greater corre pondence of levels of blood con tituent between identical twins than between siblings On the ba is of the e ob ervations it is u gested that when the individuals who are most vulnerable to cardiovascular di ease have been identified it be a certained whether levels of blood pres ure and lipoprotein in the blood are at lea t in part geneti cally determined

A genetic evaluation should be a part of any epidemiological tudy A number of simple test factors exi t that enable the investigators to detect gross genetic differences within the group or groups being studied

The application of genetic techmics to cardiova cular di ease may be divided into three broad areas

1 Gathering of Information — Com plete family hi tory (including infant deaths) an objective description of the subjects physical characteristics identi fication of the subjects with their known relatives pre ence or absence of con anguinity hi tory of exposure to radia tion In countries where regi tries exi t these hould be utilized

2 Mass Screening Laboratory Tech nics — Electrophoretic analy is blood typing pecific antigen antibody reac tions chromotography urinary amino acid excretion patterns (urinary tests for alcoptonuria cy tinuria galacto uria and pentosuria) enzyme determinations cytological and sex determination Par ticularly u eful in term of mass surveys would be the application of carefully designed overload tests to detect the latent state or the carrier state of cer tain metabolic abnormalitie

3 Studies of special group uch as genetic i olates and twin family aggre gate

Lilienfeld has recently publi hed re sults on a methodological problem in the tudy of familial a gregation of disea e In particular he inve tigated the application of a binomial test to determine the consi tency of ob erva tions with a reces ive gene hypothesi His re ult indicated that this method had a low ability to discriminate be tween genetic and non genetic hypo theses In accord with the publi hed opinions of everal geneticist he drew attention to the difficulties and pitfall in determinin whether a disea e i inherited

EPIDEMIOLOGIC METHODS IN CURRENT CARDIOVASCULAR DISEASE RESEARCH

Ralph S Paffenbarger Jr MD FAPHA and D E Kruger

DURING the six month period ending in March 1959 we have had opportunity to review a series of epidemiologic studies of cardiovascular disease currently under way around the nation Twenty one of these studies deal with some aspect of hypertension or arteriosclerotic heart disease and thus their study method may be of interest to the members of this conference An overall view of these study methods is given as well a brief descriptions of each of the 21 studies Abstracts of eight which perhaps have been less widely discussed than the well known endeavors at Framingham All any (to exemplify the range of methods employed and are incorporated in the body of this report Abstracts of the remaining 13 are included as an addendum

Study Methods

The application of epidemiologic methods to the study of arteriosclerotic heart disease (ASHD) and hypertensive heart disease (HHD) is taking three approaches descriptive analytical and experimental (1) In the descriptive approach observations on recognized disease are made in terms of chronologic and geographic distributions and the characteristics of patients Personal attributes of patients are contrasted with similar attributes determined from census figures or some other available source for residents in the patients communities (2) In the analytical approach independent variables are identified and related to the occurrence of disease The frequency of specific host or environmental factor and the frequency of disease each determined Population being studied are divided into those with and those without disease and in each group the proportion with common personal attributes or exposure ascertained Also the proportions of diseased and of nondiseased populations that engage in a common practice encounter similar incidents or are exposed to similar potential risks are measured (3) In the experimental approach human volunteers are induced to change their habits or environmental factors are altered and the effect of these changes on disease is measured

Regardless of the approach used the purpose is to determine whether individuals characterized in one way such as by a physiological or socioenvironmental factor are differentiated in a second way as by a disease For example one might determine whether a difference in the frequency of coronary heart disease (CHD) exists between a group with premature presbyopia and another group without it The essence of the approach is comparison and it is encouraging that investigators are greatly concerned with standardizing their observations and accurately classifying persons by the presence or absence of two variables the factor in question and the disease in order to make valid comparisons possible The scientific requirement of assessing the socioenvironmental variable independent of the clinico-laboratory variable is being met For the most part attention is given to other influencing variables through selection

of study subjects or through adjustment by accepted statistical technics Uncertainties in diagnosis of disease lead to use of probable or borderline classifications and most socioenvironmental factors are measured on a gradient scale Thus comparison of the disease variable and the socioenvironmental variable usually is not limited to a two by two correlation

The search for association between either ASHD or HHD and any of a number of host or environmental factors uses one of three methods First contemporary studies of diseased and disease free persons are providing snapshots or prevalence figures of the specific factors under study Second studies that are longitudinal in time are picturing flashbacks to an earlier period by measuring (through interview past medical record and similar data) the proportions in the disease group and in the disease free group that have experienced the same specific factor Last longitudinal studies are following individuals through a period of time in motion picture fashion and by means of appropriate clinico laboratory tests are making initial and successive determinations of the frequencies and magnitudes of the diseases and the factors

Populations being studied include (a) hospital or clinic patients (b) closed populations in institutions and (c) groups of persons in communities at large The populations ordinarily are chosen to meet a specific requirement of the study design

The abstracts of study methods reviewed here are necessarily brief Responsibility for omissions inconsistencies or inaccuracies in these abstracts is ours and not that of the investigators who supplied the information

Current Studies

1 Navajo on Reservation—The first study to be described is being conducted out of the Western Navajo Hospital in Tuba City Ariz The frequencies and distribution of cardiovascular diseases (CVD) particularly coronary heart disease (CHD) among the Navajo are being observed Specific aims are to determine (a) the prevalence and incidence of CHD (b) the serum lipid patterns of adult Navajo males (c) the make up of the Navajo dietary and (d) the geographic and demographic characteristics of Navajo subgroups on the reservation These endeavors were prompted by prevailing clinical impressions and published reports to the effect that the Navajo experience less CHD than the white or Negro races The design of methods includes the examination of 150 adult Navajo males who were considered healthy and without clinical or laboratory evidence of diabetes renal disease or thyroid disease Clinico laboratory examinations of snap shot type are being performed and for comparative purposes similar measurements are being made on a selected series of healthy white males seeking routine medical checkups in a medical clinic in Albuquerque In addition the heart and aortas of Navajo and clinic patients coming to necropsy are being examined for atherosclerosis (Approximately 50 per cent of the Indians who die in the Fort Defiance Navajo Medical Center or in the Western Navajo Hospital come to necropsy)

2 An example of the motion picture method applied to an open population is the study in Evans County Ga The study has been activated in search of precursive factors of atherosclerosis and its sequelae The total county census (by age sex race address and place of birth) has been determined from vital records list of utility subscribers newspaper solicitations and house to house canvasses The census is being kept current by periodic rechecks using these same counting devices Morbidity

and mortality data are obtained through phy ician vital record and ho pital data The county with a population of 7 500 and a two to one white to Negro di tribution is largely rural and i erved by two practicing physicians One of the phy ician in the spon or an l princi pal inve tigator in this tudy and the other cooperates clo ely Marked rap port exi t among the phy ician and their patient who comprise e entially the total county population No rop ie are requested on the death of each county re ident and are performed by a con ulting pathologist on approxi mately 50 per cent of dec dents

Relative rates of CHD by race and ex groups are bein determined longi tudinally from (a) phy ician ho pital autopsy and vital record and (b) successive censu es of Evan County Thi phase of tudy will continue through calendar year 1960

Blood specimens for erum lipid de terminations are being drawn from ap proximately 1 200 adult li ted on the Evan County cen us regi try Subjects are cho en throu h u e of a stratified samplin technic Laboratory testing of specimen permits compari on of lipid level by age ra e sex and sea son of the y ar in which the amples were collected

For one physician s office practice all patient aged 35 years and over who eek medical advice or treatment for any illness are being followed over a five year period (mid 1958 through mid 1963) for the occurrence of CHD To the degree that a bu y practi e permits the following data are bein recorded on each patient at least once annually (a) family and personal his tory of heart di ease (b) result of a general phy ical examination and (c) findin from erum cholesterol and alpha and beta lipoprotein test When patients do not return within a year they will be contacted and lipid deter mination repeated a a minimum ex amination All overt attacks of CHD and deaths from this cau e will be recorded as they are recognized Bien nially the health tatu of *each partici* pant will be reviewed through telephone or personal contact Through record of uch repetitive ob ervations and labora tory *determinations it is expected that* ome of the precur ors of CHD *may* come to light

The influence of ex race and tres factors (physical and psychological) on serum lipid level of children from birth through preschool ages is being determined Umbilical cord blood am ples are being collected at mo t deliv eries in the county and repeat blood amples are drawn at ix month in terval These specimens are being tested for levels of cholesterol alpha and beta lipoproteins, and the lipid mobilizing factor The race ex and birth weight of each infant are re corded together with weight and illness hi tories at each ix month interval

Studies of chool aged cohorts are patterned after the newborn tudies with effort being made to enli t all school children in the county More than 95 per cent have received parental approval to participate and are being entered in the tudy as rapidly a labor atory facilities permit Repeat blood samples are being drawn at annual in tervals and pecial interest centers on the influence of puberty on erum lipid level

3 The napshot method i being u ed at Loui iana State Univer ity School of Medicine in tudy of athero clero i Procedures have been tandardized for taining artere with Sudan IV and for preservin them in flat tran parent durable pla tic ba s Also a method of grading human aorta by which dif ferent pathologi ts secure imilar result has been developed and used to estimate macro copically the extent of fatty treaks fibrous plaques and complicat ing lesion (hemorrhage ulceration

thrombo is and calcification) Current tudies eek information on pathogenic mechanisms through description of aortas and other arteries from necrop ies on individuals aged one year and over Specimens are received from general ho pitals and medico legal erv ices in New Orleans Guatemala Puerto Rico and Colombia Special attempts are made in these geographic areas to necropsy all deaths regardless of cau e All aortas mo t coronary arter ie and more recently cerebral arteries are graded as to intimal lesions Phvsi cal studies (photographic light refrac tion and colorimetric) and chemical studies (quantitative and qualitative determinations of lipid) are in progress on a sample of pecimens to (a) develop a grading scheme that does not require per onal judgment and (b) search for age ex and racial differences in patho logic lesions An endocrine project in cluding urine a says is being developed to permit correlation studies with ath erosclerotic lesions

As a econd study observations on zoo reared baboons have suggested that this widely prevalent ape which is fir t order below the anthropoid might lend itself as an ideal experimental ani mal for atherogenic studies Hence an African expedition was undertaken in the summer of 1958 to obtain baboons from their native habitat A total of 163 animals was captured and sacrificed for pathologic examination Specimens permitting estimation of chronological age and degree of atherosclerosis were hipped to New Orleans for study (Age e timates are being made from kull teeth and bone pecimens together with measurements of body weight and size)

4 Out of the Georgia State Health Department a motion picture study of two circumscribed populations is in progress Since October 1957 serial observations have been made on resi dents of two mona teries in tudy of dietary regimens as they may relate to arterio clerotic heart disease (ASHD) One monastery quarters members of the Trappi t order whose religiou dictates require a meat free lactovegetarian diet The second monastic population com prises Benedictine monks who are om nivorous and consume a diet e entially comparable to that of citizens at large in the United States Quantitative and qualitative dietary records are collected on elected fast feast and regular days in order to compute average intakes per monk per day Yearly clinico laboratory examinations and medical records during any period of ho pitali zation permit evaluations of illne ses including ASHD Blood specimens drawn quarterly are subjected to a battery of tests for lipid and protein determinations Participation in this ongoing study is voluntary with more than 95 per cent of the Trappi t com munity and a comparable percentage of residence stable Benedictines enrolled

Eighty two Trappists ranging in age from 20 to 80 years (median age=35 years) are participating The e monks live rigorou lives in primitive physical etting without modern conveniences Their work is largely of heavy manual types which is inter per ed with seden tary hours for meditation There is es entially no verbal communication among the monks On days elected for determination of diet intake each monk keeps a record of his consumption by noting during meals the amounts and types of food inge ted Uniform erv ings and the u e of tandard poon sizes facilitate accurate reporting Tobacco and alcohol are not u ed by these monks

Sixty five Benedictine monks of an older age range (median age=40 years) than their Trappi t peers are partici pating They live in modern dormitory type structures engage in relatively less phy ical exercise and are largely a teaching order Their diet permit little freedom of choice qualitatively but

contrary to that of the Trappi t - allows for more quantitative election A food model demonstration is pre ented at the monastery to a si t the monk. in making quantitative e timates of their intake A small proportion of members of this order u es tobacco an l a ome what larger proportion u es alcohol

5 A combination of snap hot fla h back, and progres ive motion picture methods i in u e at Beth El Ho pital Brooklyn N Y In progres over the pa t two years this study is de igned to determine whether pecific somato types are as ociated with a coronary diathesis and if so for what rea on Members of a fraternal organization are invited to a cancer and heart di ea e detection clinic for specific clinico lab oratory te ts that permit classification by body type coronary heart di ea e tatus socioeconomic stratum and cholester olemia and estrogenuria levels The base population from which subjects volun teer to participate consi ts of 35 000 residence stable Brooklyn males who carry health insurance . Participants are somewhat health con cious adults who largely lead a edentary life and eat high fat diets Sixty per cent are salesmen and 95 per cent are married They are queried as to dietary and social habits and cla sified into types of body build by the ame examiner A econd examiner evaluates their car diac status through admini tration of a medical history physical examination and electrocardiogram (ECG) tracing Their attack rates of CHD are being as essed through (a) annual reexamina tions and (b) reports on cardiac mor bidity and mortality from their health insurance plan which includes phy i cian and hospital coverage One hun dred elected subjects in each of the three basic omatotypes (ectomorph mesomorphs and endomorphs) are being examined for estrogen level by analysis of 24 hour urine ample

As an independent tudy the degree of coronary atherosclero is and the type of body build are being a. essed for all individuals dying suddenly and coming to medical examiner autopsy in We t che ter County N Y The collection represents a 10 year experience and compri es largely deaths from automo bile accident

6 Sometimes referred to a a human population laboratory studies in prog re s at the Univer ity of Michigan School of Public Health maintain a current inventory of people place and things Over an 18 month period nearly all residents of Tecum eh, Mich and adjacent residential area have been characterized by demographic and other factor The prevalence of 11 chronic di ea e conditions has been de termined for this group through elf administered questionnaire form The total population of approximately 8 300 person has been identified by hou e hold (N=2 400) familial and kindred (N=3 400) aggregation An additional 1 000 persons from neighboring com munities who are relevant to the blood line aggregates have been identified

Through even con ecutive monthly reports received by mail from each hou ehold new occurrences of illnes have been determined Al o tudy ha been made of the phy ical facilities and of the receptiveness of lay and medical groups to future more inten sive studies in this population The collected data have been analyzed a a lead eeking device and to determine the suitability of the population for ub equent epidemiologic tudy of a variety of chronic di ea e entities On the ba is of the e analy es the inves tigators are satisfied that the commu nity lends itself to pro luctive future tud ince (a) the ingle large indus try in Tecum eh is relatively table and the population i nonmigrating (b) adequate numbers of individual over the entire a e pectrum are avail able (c) a high prevalence of numer

ous chronic diseases exists and (d) new cases of CVD occur with a frequency which permits testing of many hypotheses over several year period

Early identification of individuals as to their susceptible or immune status in reference to heart diseases through both nap hot and motion picture studies is under way (Other chronic diseases will be studied in similar fashion) Specific aims include (a) identification of individuals with heart disease and associated condition (b) search for associations between factors of host environment and specific types of heart disease (c) analysis of data by kindreds in search of familial influences and genetic patterns (d) description of the frequencies and distribution of cerebrovascular accidents (CVA) and determination of their relationship to heart disease (e) examination of heart disease patterns for relationships among congenital rheumatic arteriosclerotic and hypertensive heart disease and (f) initiation of similar studies of chronic disease other than heart disease Procedures entail the examination of Tecumseh inhabitants resident of surrounding area and kindred in neighboring communities (N=approximately 9 500) Method include taking detailed medical histories by trained lay interviewers review of these histories by physicians who perform physical examination and laboratory examinations

As another study blood pressure level among Bahama Negroes have been measured to determine prevalence ratios of hypertension and to compare the findings with similar data available for Negroes living in the United States One study is based on the clinical record of the single physician on the Grand Bahama Island and pertains to approximately 60 per cent of the inhabitant

A third study relate to blood pressure determinations made by an epidemiologist and medical students from the University of Michigan on 3 000 individuals chosen as a probability sample of Nassau City on Providence Island Demographic social and cultural data have been collected on these subjects large proportion of whom are Negroes Drinking water samples from elected communities have been collected for sodium determinations since the water frequently is brackish and association between water of high sodium content and hypertension will be looked for

7 At the Johns Hopkins University School of Medicine and School of Hygiene and Public Health two different methods of study and two different types of population are being used in search of factor associated with CVD Since 1916 medical students at the Johns Hopkins University have been used as subjects in a study designed to identify those characteristics which may be of value in predicting and in preventing an early onset of CVD To date nearly 1 000 student have been classified by a variety of genetic physiological psychological and metabolic characteristics in search of those traits which are associated with CHD or HHD The CVD heritage of each student is assessed through family histories taken on parent grandparent uncle and aunts by the student themselves in their third and fourth years at Hopkins On the fifth and tenth anniversaries of graduation each student is reevaluated by mail questionnaires concerning his health status and sociophysical habits The health status of his parent also is redetermined Under the assumption that students experience greater risk of developing CVD if they have an unfavorable CVD heritage constitutional differences between low and high risk student group have been identified Based on observations to date a four way grouping of healthy students according to parental history and student characteristics has been proposed as a basis for electing highly

u ceptible individual The individual po itive traits in this grouping in clude (a) higher erum chole terol levels (b) nonectomorphic body build (c) higher blood pres ure level (d) tachycardia and (e) blood pre sure hyperreactivity to cold or exerci e A tudent with two or more such po itive traits is cla ified as having po itive individual characteri tics The parental po itive traits signify that one or both parents ha a history of coronary or hyperten ive di ea e Follow up data on health will be related to these char acteristics

As an independent study the death certificates of Baltimore residents aged 45 years and le who died between 1950 and 1959 have been categorized by cause of death in earch of factors predi po ing to ASHD Subjects with death ascribed to ASHD have been sub cla ified into one of three categories following validation of death certifica tion through review of hospital phy i cian and autopsy records These cate gories are (1) definite ASHD (2) uncertain ASHD and (3) definitely not ASHD In the period under tudy death certificates with diagno es of ASHD included nearly 200 ubjects with a validated diagno is of ASHD (Group 1) 250 with uncertain ASHD (Group 2) and approximately 100 with diseases other than ASHD (Group 3) All other Baltimore decedent in this age cla s (15 year and less) except those dying of accidental cau es are cla ified into a fourth category (Group 4) Individuals who e death was a cribed to ASHD (Group 1 and 3) are then matched by age ex race and date of death on a one to one basis with individuals cla ified a having died from other than ASHD (Group 4) Survivor (pou es or sibling) of the deceased are interviewed by nur es mak ing home survey for pecific and de tailed information on family hi tory of ASHD alcohol and moking other disea e marriage and reproduction and psychic and physical stre s Through cro s correlation analyses tho e factors of host which are associated with early death from ASHD are being ought In search of pr cursors of ASHD erum cholesterol and serum uric acid deter minations are being made on a ample of the decedents children and pouses in each of the four groups

8 Two tudies are being conducted by worker affiliated with the Health In urance Plan of Greater New York and Columbia University College of Phy icians and Surgeons The fir t is aimed at determining the influence of female gonadal function on the devel opment of CHD The method employs the measurement and compari on of CHD prevalence in oophorectomized and in a control group of non oophorecto mized hysterectomized women White female gynecological ward patients aged 45 65 years from the Columbia Pres byterian and Mt Sinai Ho pitals are being included in the tudy Other ho pitals will be added if nece ary to realize the population of 700 oopho rectomized and 1 300 non oophorecto mized ubjects e timated to be needed in order to determine whether there i a difference in CHD prevalence Te t and control group are being matched by (a) period of operation within three year grouping (b) age at opera tion and (c) nationality or country of origin Patients with hypertension or diabete at time of operation are elimi nated from the tudy Study ubject are identified through medical record review and then contacted through one or another of the following methods (a) telephone (b) attending gynecolo gi t (c) ocial ervice exchange (d) return United States mail (Form 3547) (e) Welfare Department or (f) vi its by a retail credit agency When noti fied of a death the investigator obtain a copy of the death certificate Survivors are invited to the ho pital for medical

and laboratory examinations A history of estrogen administration is obtained from the patient's family physician The criteria for diagnosis of CHD rest largely on history of episodes and current ECG tracings The study will continue until interpretable results are obtained

The second study is that of CHD survivorship and repeat attacks It has been activated only as a pilot undertaking thus far utilizing new cases reported from three HIP Medical Groups Patients are invited for examination by a single physician and for appropriate laboratory examinations Serial medical checks are planned at six month intervals for two years and biennially thereafter Attention will be given to clinical manifestations that develop as well as to mortality

Discussion

In general the studies reviewed here employ methods which have been developed and extensively applied in the study of infectious diseases The process is that of measuring and comparing the frequencies and distributions of disease within defined populations The aim is to identify or unmask those factors and conditions that cause disease In regard to causation it is recognized that the inability to see the dynamic processes of pathogenesis in human subjects calls for use of the *epidemiologic* method and the inductive reasoning on which it depends

Of the three methods being used in search of associations between cardiovascular disease and host or environmental factors—termed snapshot flashback and motion picture for convenience of description—it is generally agreed that motion picture studies provide the most comprehensive and accurate data The three study types are complementary however and are most effective when they are used in combination

The investigators interviewed are aware that the mere demonstration of statistical association between a given factor and a given disease does not establish the link of causation between the two events Rather such an association simply indicates that a change in the frequency or magnitude of one event is accompanied by a change in the frequency or magnitude of the other A given event shown to be directly associated with a given disease may represent only an index of a second event which is in fact a true cause

Procedures to distinguish temporal association from causal relationship must be designed to fit specific situations and conditions Such differentiation requires a thorough knowledge of biologic concepts of the disease together with the conduct of studies that would test specific hypotheses Procedures would seek to verify by further facts to establish ancillary evidence to reproduce results under different circumstances or to develop alternative hypotheses

Uncertainty exists as to whether the factors presumed to be related to CVD represent primary or secondary etiologies—that is are they definitive cause or in contrast do they provoke clinical attack in individuals harboring a primary cause? Do such factors as hypercholesterolemia hypertension obesity and the like comprise definitive or only predisposing etiologies of CHD? These questions thus far unanswered may prove analogous to the interactions between primary and secondary etiologies in acute poliomyelitis In this disease three immunologically distinct viruses comprise essential causes and such factors as pregnancy oropharyngeal surgery and the intramuscular inoculation of antigens have been established as contributing causes

Current and Proposed Study Factors

The 21 studies which we have reviewed are measuring a variety of environmental and physiological characteristics in addition to those on which information is obtained in the course of a routine diagnostic examination—medical history, social history, physical examination and laboratory tests. Table 1 shows a partial list of these additional factors, the number of investigators currently measuring each factor and the number of other investigators among the 21 principal investigators who were proposing but had not yet begun to measure the respective factors at the time of our review in early 1959.

Decision to measure a particular factor implies that some hypothesis about that factor and the occurrence of disease is being tested. For any given factor different measurements are being made from study to study.

Diet is the factor of interest to the largest number of investigators; ten are currently measuring diet and seven others propose to do so. Four are now using some measure of psychic stress and five others plan to measure it.

The items physical stress and occupation require some explanation. Physical stress refers to the administration of some test of reaction to exertion such as an ECG after exercise, whereas occupation refers to a job classification as an index of physical activity.

Environment change as used here means an attempt to alter a specific characteristic, e.g., dietary intake, and to measure the effect of this change on the occurrence of disease. A decision to undertake environmental change rests not only on confidence that an association exists between an environmental characteristic and occurrence of disease but also on the idea that a change in the environment will be accompanied by a change in the occurrence of disease. The problems of measurement of the factor still exist and may be made more difficult because of the fact that the investigator has induced an ecologic change.

It is apparent from this list of factors being measured in current and proposed research that the subject areas of measurement selected for attention in this Conference on Methodology are of immediate and major importance in epidemiologic studies of CVD.

Table 1—Environmental and Physiological Factors Measured in 21 Selected *Population Studies*

Factors Measured	Population Studies	
	Current	*Proposed*
Psychic stress	4	5
Physical stress	3	2
Dietary	10	7
Occupation	8	0
Environment change	1	2
Lung function	3	0
Skin fold	5	0
Clotting	2	2
Endocrine	5	1

Summary

The methodologies being employed in a series of epidemiologic studies have been reviewed. By means of measurement and comparison the aims of these studies are to determine whether persons manifesting specific physiological or socioenvironmental factors experience a different risk of cardiovascular disease than do persons without such factors. Associations are sought between a specific disease and a specific factor through (a) contemporary studies providing a snapshot of the two events, (b) chronological studies picturing flashbacks to an earlier period and (c) long term studies of progressive motion picture type. Groups under study include closed or open populations that are chosen at random or selected on the basis of some preexisting condition.

It is recognized that the success of both current and propo ed epidemio logic tudies will rest on standardized ob ervations and on precise classifica tions of persons according to the pre ence or ab ence of two variables a pecific factor and a specific disease Follow up studies will attempt to dis tinguish between a sociations that are only tatistical and tho e that reflect a cau ative relation hip To this end epidemiologic studies will complement clinico laboratory efforts by providin collateral evidence by verifying ampli fying or modifying prevailing concepts or by developing alternative hypotheses It is anticipated that application of epi demiologic methods to the tudy of chronic disea es will lead to evidence consistent with a causative hypothesi as have such methods in the study of acute diseases

Addendum

9 Framingham Mass—This longitu dinal tudy began during the period of 1948 to 1950 and has run continuou ly to date Serial ob ervations have been made on over 5 000 individual or 69 per cent of an initial randomly cho en sample that repre ented two third of the Framingham population aged 30 to 62 year Biennial medical hi tories physical examinations and laboratory tests have provided the data for tudy Peports from local practicing physi cians and ho pitals have complemented the e record The study initial aims were to obtain descriptive information on CVD and to measure prevalence and incidence of the e di ea es in the popu lation Secondary purposes were to test elected hypothe es concerning cau a tion of heart disease the hypothe es being con tructed from clinical impres sion or the epidemiologic findings of others To date major effort ha been directed to ASHD and HHD and to a ociations between these di ea es and pecific factors of host Foremost among these factors have been hyper cholesterolemia hypertension and obe ity More recently other factors have been added and include dietary habit alcohol consumption tobacco usage edu cational levels lipoprotein measure ments and di trict of residence in Framingham Plans call for exten ion of the tudy over at lea t ten more years

10 Connecticut State Health Depart ment—Studies began early in 1957 with the initial aims of (a) measuring the prevalence and incidence of CHD and CVA in Middle ex County and (b) te ting specific hypothe es concern ing causation of myocardial infarction (MI) a related to particular dietary habits and to ocial and per onality correlates of stress Ca finding has been achieved through report from practicing physicians and ho pital coupled with death certifications A 10 per cent probability sample of the popu lation was queried through Bureau of Cen us interviews to provide population e timates for rate denominators an in dependent estimate of clinically manifest CHD and control eries for the com pari on phases of the study i e the nu tritional and sociopsychological phases

The ociopsychological a pects of the tudy contrasted a sample of white male patient aged 35 64 year who survived an attack of MI with an equal number of patients suffering from an acute evere illness other than heart di ea e and matched with the test group by (a) age to within five year (b) race and ex (c) occupational level and (d) ethnic origin traditionally similar to that of the te t subject The e tudies continue and are currently directed at refinement of both hypotheses and tools of mea urement

11 New York State Department of Health—A long term project began in 1953 a repetitive ob ervations on nearly 2 000 male Civil Service employee aged 39 59 year from the Albany

area Participants represented 89 per cent of the population invited into the tudy Primary objective have been (a) to ev aluate established methods of early detection of all forms of heart di ea e (h) to evaluate new techniues for thi purpose and (c) to look for etiologic factors of CHD Annual phy i cal examinations and medical hi tories by phy ician as well a self administ tered questionnaires have provided the data for tudy Clinico laboratory meas urement have permitted a wide earch for factors a sociated with all types of CVD Special empha is has been placed on the study of potential nutri tional influences on the e di eases The tudy proceeds in tandardized fa hion with more inten ive clinical observations being made on sub ample of the study population

A econd project began in early 1959 and continues to date It compri es a tudy of con ecutive autop ies from a general hospital and the comparison of cardiac pathology with ante mortem characteristics and environmental ex po ures of the decedents The principal purpo e i to search for etiologic factors of coronary occlu ion and MI Obser vations at necropsy include measure ments of the lumens and thickne es of coronary e sel Ob ervation concern ing the autop ied subjects are made through medical tudent interview with a clo e relative of the decedent Other ocial and environmental detail are ol tained from the u ual family phy i cian and life insurance medical records of the decea ed Selected characteris tics being tudied include nutritional factors usual occupation wei ht alco hol con umption tobacco u age and o forth Compari on on these charac ter tic are made between individual dying of heart di ea e and individual dying of other di eases It i expected that the tudy will be extended l eyond the current population of approximately 900 autop ies

A third tudy is being started which contra t by retro pective mean ca es of MI with matched control ubjects The ca e population is being obtained by a carefully developed and vig orously monitored reporting sy tem from all phy ician in Albany County Report ing includes ca es with other manifesta tions of CHD but detailed tudy is being limited to survivors of fir t in farctions Control subject matched on five characteri tics (ae ex race socioeconomic tatu and urban rural residence) are drawn from a 5 per cent census of the population It i esti mated that 500 case matched with an equal number of control will be col lected by 1961 Compari on of the e population will be directed primarily toward the variables of diet physical activity and chronic emotional tres although a number of other charac ter ti are being studied

12 Columbia Univer ity College of Physician and Surgeons Harvard Med ical School and University of Briti h Columbia Medical School—For the pa t 12 years a group of 100 sympathec tomized (Smithwick operation) hyper tensives and an equal number of un treated hyperten ives have been followed to as ess the effect of this operation on survival Pairs of test and control subjects were elected from hyperten ive clinics in New York City Bo ton and Vancouver They were matched by (a) age race and ex (b) aver age and range of blood pre ure read ing (c) cerebral symptoms and compli cations (d) cardiac ize and ECG pat tern (e) hi tories of angina or cardiac failure and (f) other factor including degrees of proteinuria eye ground chan es and renal damage Each of three investigators reviewed clinical and survival data on all pair in a blind fa hion at two five and ten years after ubject were entered into the tudy

Independent tudies of imilar

matched control type are being under taken at Columbia u ing groups con sisting of 25 patients each to te t specific hypotheses These groups will provide information on relative sur vival rates of (a) patients with malig nant and essential hypertension and (b) drug treated and untreated hyper tensives

13 New York City Health Depart ment—Thi project began in February 1957 to determine (a) if it were feasi ble to achieve dietary control in a free living population and (b) if such dietary management would reduce total cholesterolemia and lower coronary heart morbidity and mortality Male volunteers willing to follow tailor made dietary patterns were solicited through two new paper announcements They were included in the tudy after attend ing an orientation lecture if they ex pres ed willingness to follow a pre scribed (prudent) diet over many year perhaps until age 65 years Origi nally the study included males a ed 50 59 years but thi has since been broadened to include age classes from 20 through 59 years

When a subject enters the study a medico laboratory examination is con ducted and a comprehen ive diet his tory covering the two preceding weeks is obtained by personal inte rview with the subject and his wife The interview permits an estimate of all nutrients as well as the intake of total calories and calories from fat If the ubject is judged by clinical means to be over weight he is put on a weight reducing diet When a normal weight is achieved the subject is placed on a prudent diet that includes a fat intake providing about 30 per cent of total calories Fats are divided half and half into aturated and unsaturated types of fat (Part of the latter is given in su h forms as specially prepared margarine containing 80 per cent un altered corn oil and a milk con tructed from a homogenized mixture of fat free powdered milk vegetable fat and water)

Serum cholesterol levels are measured at weekly intervals at the outset to establish a base line which is computed as an average of two or more determi nations within 10 per cent of the lowe t Follow through is attained by (a) annual medical examinations with ECG trac ings (b) erum cholesterol measure ments and diet and weight checks every four weeks and (c) sessions with a board of review (phy icians) every ten weeks to discuss the individual progre s Subjects provide medical data at the ten week check and hospital in formation where it exists complement this Subjects are told that they will be followed personally until a e 65 years and thereafter through Social Security records

14 University of Pittsburgh Graduate School of Public Health—The mortality experience in (1) the Arsenal Health District of Pittsburgh during the inter val 1951 1956 and (2) Donora Pa from 1948 to 1957 has been reviewed Mortality has been examined in rela tionship to prior findings of morbidity surveys in each area (The Donora ur vey of 1948 inve tigated the health effects of mog exposures in October of that year The Arsenal urvey was undertaken to measure the frequency of chronic illnesses and medical care in 1951) Together with these mortality studies the surveys of these populations have permitted prevalence estimates of various chronic conditions including heart diseases Findings have convinced the workers of a need for (a) more detailed ob ervations on recognized cases of all di eases and (b) a better understanding of the timing of onset of overt heart di ea e and its progres sion Forthcoming tudies in a group of industrial employees will give atten tion to these problems

15 Presbyterian St Luke s Ho pital

—A five year tudy of heart di eases among a large group of industrial em ployees began in the fall of 1957 with particul ir emphasis on CHD Study ubjects were men aged 40 55 years who had been employed two years or more in a Chicago electronic indu try and who on review of the company medical record were believed not to have had either MI or angina pectoris when the study started A total of over 3 000 men was randomly cho n from the complete ro ter of company em ployees and invited to participate Over 2 100 (70 per cent) complied have been examined and are now in the econd round of examinations The aims are (1) to determine the cardiovascular status of ubjects at the time of the initial examination (2) to measure in cidence of heart disease through four annual reexaminations and (3) to re late the incidence of heart di ease to various physiological measurements and other characteristics of the subject Data gathered at the initial examina tion included (a) a family hi tory pre pared by the subject (l) a medical hi tory and physical examination by one of 2o volunter physicians as isting in the tudy (c) clinico laboratory te ts including somato typing with photog raphy (d) diet a sessment by detailed interview with the subject and a ques tionnaire completed by the spouse (e) hy ical activity measurement by analy m of job requirements and an inter view concerning off the job phy ical ex ertion and (f) personality traits deter mination as revealed by the Minne ota Multipha ic Personality Inventory These procedure are l eing conducted in facilitie at the plant and require about two half days for which the ub ject is given time off with pay

16 Tulane University—Since 1911 the influence of hot and humid (ul tropical) environments on phy iologic and pathologic respon es in man ha been under tudy Observation are being made both in hospital wards and in experimental chambers using normal ubject and patients with chronic con ge tive heart di ea e Mea urements of cardiac function are being contra ted between study population and temporal compari on are being made within the e populations

17 South Carolina College of Medi cine—Clinico laboratory procedures have been developed and standardized to per mit screening of large numbers of ub jects for (a) blood lipid levels (b) whole blood coagulation and (c) in travascular agglutination of erythrocytes (ludging) Interrelation hips among the e variables are being sought for everal contra ting groups including (a) elected di eased and normal popula tion and (b) samples of white and Negro residents of metropolitan Charles ton A batterv of lipid tests are being run on all blood erums including those for cholesterol pho pholipid tri glyceride and alpha and beta lipopro teins Microscopic ob ervations photo graphs and closed circuit televising of the capillary circulation in the bulbar conjunctiva allow estimation of the de gree of erythrocyte agglutination and arteriolar plugging with ludged ma e Blood coagulation is measured by con ventional technic

18 California State Department of Health—In 1918 a total of 577 healthy individual aged 50 years or more were selected from 813 regi trants who vol unteered to participate in a tudy of nutrition as related to aging Selection from the regi trants trove to include only individuals who were phy ically and mentally capable of participatin in good health not under a phy ician care within the three prior month *and not food faddi t* Selection attempted to achieve an equal ex di tribution and a range of age and eco nomic cla es Initial tudy of thi group included (a) a nutritional hi tory and a record of seven day food

intake (b) a detailed medical history and complete physical examination and (c) a series of laboratory results from blood and urine analyses and from chest x-rays bone density determinations and vaginal (Papanicolaou) smears Follow up physical examinations and dietary evaluations of as many subjects as were available were made in 1952 and again in 1954 Data that have been analyzed pertain to mortality morbidity and disability (both for CVD and for total disease) in relation to the original (1948) physical findings blood analyses and diet patterns The health status of subjects still available for examination and interview is being reevaluated after a total of 11 years of observation

In 1951 a multiphasic screening examination was given to 1 000 longshoremen who volunteered to participate out of a total of 6 000 such workers in the San Francisco Bay area Tests included measurements of age height weight hearing blood pressure hemoglobin blood sugar glycosuria albuminuria a chest x-ray and an ECG tracing The subsequent mortality of the 4 000 volunteers and the 2 000 nonparticipants has been followed through death certificate analyses and union health insurance records This study continues as a routine operation offering a potential for testing a series of hypotheses of causation

A health survey of a representative sample of Californians was conducted in 1954 1955 whereby information was obtained for nearly 32 000 individuals by Bureau of the Census interviewers A total of 250 individuals (150 males and 100 females) gave history of some form of CHD A substantial proportion of these individuals was matched with disease free control subjects of the same age and sex chosen from the survey population Interviews were held with diseased and control subjects to determine the relative frequencies of various characteristics that might be related to CHD (Next of kin were interviewed where subjects in the sample had died) Special attention was given to (a) smoking habits (b) presbyopia (c) physical exertion at work (d) participation in athletic events (e) occupation (f) urban versus rural residence and (g) native versus foreign birth

19 Mt Zion Hospital San Francisco Calif —The role of specific behavior patterns as they may predispose to CHD among selected population groups is under study In general these efforts measure independently (a) personality and behavioral patterns and (b) historical experiences with CHD Subjects many of whom are industrial executives were selected if they gave evidence of highly developed aggressiveness competitiveness and a tendency to accelerate all activities or if on the other hand they seemed to lack these attributes Evidence of previous experience with CHD was obtained from medical histories and ECG tracings Competitive subjects (N=83) were matched with noncompetitive subjects (N=93) by similarities in age race ethnic group diet height weight and the amount of physical activity required by their jobs A total of 12 unemployed blind subjects also were studied The latter resembled the noncompetitive group in personality pattern but had the complicating factor of continual anxiety At the time of observation electees first were categorized by one examiner as to whether their behavioral pattern which had been elected to represent the extremes of contrast between driving and easy going personalities were completely or incompletely developed (This was done for purposes of subclassification) A detailed medical history was taken and a physical examination performed Then a second examiner drew blood for determinations of cholesterol

and clotting time measured bleeding time and took ECG tracings A third examiner gave detailed instructions that would permit selectees to record qualitative and quantitative information on dietary intake by daily diary technic for one week

Short term studies on small groups of CHD patients and selected control subjects are under way to refine current technics and to develop new and better methods Endocrine CHD hypotheses are being tested through utilization of data from urinalyses Other studies now in progress are designed to measure personality traits by objective means A lie detector that simultaneously records amplitude and rate of respiration body movement and cardiac function is under study Also a psychophysiological test is being devised in search of a predictor of the occurrence of CHD in specific groups of individuals

20 North Dakota—In 1956 1957 a longitudinal study of CHD was started in a six county area surrounding Grand Forks N D to determine the feasibility of certain investigative methods and to test specific hypotheses concerning causation of this disease (This area was selected for study because vital records had indicated that North Dakota reported the lowest death rate from CHD in the nation) Patients developing acute manifestations of CHD either as new or recurrent events were reported by practicing physicians to the study center as the primary case finding device Also physician provided clinical and ECG findings on their CHD patients to assist a review committee of internists in deciding whether reported cases should be considered CHD for purposes of the study and in classifying them into subgroups Monthly visits were made by an epidemiologist to each physician in the study area and bimonthly visits were made to physicians in areas bordering the six counties to improve the degree of reporting and to collect collateral information Hospital records and mortality statistics were reviewed periodically to check the completeness of the case finding method A 10 per cent probability sample of dwelling units was chosen and residents therein were interviewed through Bureau of the Census enumerators for demographic and selected personal characteristics These characteristics included data on occupation smoking and food habits as the principal areas of interest and were determined through personal interviews with all males aged 35 years and over who came into the probability sample A single dietitian made detailed dietary assessment of each recognized CHD patient together with such assessments of two age matched control subjects chosen for each patient from the probability sample Attempt was made to establish the dietary pattern of patient for the month preceding overt disease and of control subjects for the month preceding the interview If the CHD patient had died his wife or nearest kin was interviewed as in such instance were comparable relatives of *the matched control subjects Thereafter* standardized procedures were followed in estimating qualitative and quantitative intake of specific nutrients

21 Chicago Board of Health—An ongoing study has been conducted in a Chicago utility company in search of factors of host and environment that predispose to or precipitate cardiovascular renal morbidity and mortality particularly ASHD and HHD The health status country of birth social class and occupational experience of 7506 employees aged 50 59 years (96 per cent of the plant employees in this age class) were determined as of January 1954 from preexisting records During serial observation from annual physical examinations conducted through plant facilities a series of determinative analyses is in progress (In

intake (b) a detailed medical history and complete physical examination and (c) a series of laboratory results from blood and urine analyses and from chest x rays bone density determination and vaginal (Papanicolaou) smears Follow up physical examinations and dietary evaluations of as many subjects as were available were made in 1952 and again in 1954 Data that have been analyzed pertain to mortality morbidity and disability (both for CVD and for total disease) in relation to the original (1948) physical findings blood analyses and diet patterns The health status of subjects still available for examination and interview is being reevaluated after a total of 11 years of observation

In 1951 a multiphasic screening examination was given to 1 000 longshoremen who volunteered to participate out of a total of 6 000 such workers in the San Francisco Bay area Tests included measurements of age height weight hearing blood pressure hemoglobin blood sugar glycosuria albuminuria a chest x ray and an ECG tracing The subsequent mortality of the 1 000 volunteers and the 2 000 nonparticipants has been followed through death certificate analyses and union health insurance records This study continues as a routine operation offering a potential for testing a series of hypotheses of causation

A health survey of a representative sample of Californians was conducted in 1954 1955 whereby information was obtained for nearly 32 000 individuals by Bureau of the Census interviewers A total of 250 individuals (150 males and 100 females) gave history of some form of CHD A substantial proportion of these individuals was matched with disease free control subjects of the same age and sex chosen from the survey population Interviews were held with diseased and control subjects to determine the relative frequencies of various ch
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unemployed blind subject also
studied The latter resembled the
competitive group in personality p
tern but had the complicating facto
of continual anxiety At the time of
observation electees first were cate
gorized by one examiner as to whether
their behavioral patterns which had
been elected to represent the extreme
of contrast between driving and
easy going personalities were com
pletely or incompletely developed (This
was done for purposes of subclassifi
cation) A detailed medical history was
taken and a physical examination per
formed Then a second examiner drew
blood for determinations of cholesterol

January 1958 the study was enlarged to include the entire labor force aged 40 59 years approximately 2 000 individuals) Specific aims include the testing of hypotheses concerning associations between CVD and the following host and environmental characteristics (a) place of birth (native or foreign born) (b) dietary habits and nutrition (c) marital status (d) physical activity (e) psychologic stress and (f) other factors

A second study concerns the comparison of Negroes and whites with respect to patterns of cholesterolemia and incidence of CHD Other correlates include age sex height weight occupation industry and duration of residence in northern states

A third study employing methods of experimental epidemiology is designed to measure the effect of a nutritional hygienic regimen on risk of developing CHD Several hundred middle aged men without evidence of CHD but presumed to be at high risk by virtue of high levels of (a) body weight (b) blood pressure and (c) serum cholesterol have been induced to follow a prescribed regimen and are being examined serially They are being contrasted for coronary disease with appropriately matched control subjects from the Chicago utility company

CO CHAIRMAN'S ADDRESS*

Herman E Hilleboe M D F A P H A

IN THE sessions of the conference I have not heard much about epidemiology or what epidemiologists do It seems to me we need to review the rather broad background of the things we are considering I would like to refer to Paul Sears's comment about a scientist He said Discovery and communication are the two prime obligations of a scientist An occasion such as this gives a scientist an opportunity to examine some broad issues in the light of the special knowledge and experiences of those who are not epidemiologists I hope that even though our major concern is the epidemiological method applied to various types of heart disease we shall endeavor to think in broad terms about applying such disciplines as mathematics physics chemistry and other sciences to the problem at hand

We should also bear in mind that we need to know something about biology in general and ecology in particular if we are to learn more about man's relationship to his environment We have not heard much about ecologists here but I think that epidemiologists come close to being ecologist in their method An ecologist, as you know has a viewpoint just a little different from others in the scientific field For one thing he sees man as a social being in a cultural matrix, and powerfully affected by population dynamics

Getting down to the specific point of epidemiology I am delighted with Dr Kendall's definition of epidemiology (Report of the Subcommittee on Biochemical Measurements) I would like to repeat it because it is stated perhaps better than many definitions made by epidemiologists themselves Dr Kendall said that the purpose of any epidemiological study is to evaluate the influence of diverse genetic and environmental factors upon the occurrence and severity of disease I think this is particularly pertinent in the field of heart disease where we have no demonstrated specific etiological agents

The other remark he made that struck home had to do with differences in the mean level of particular factors that might be statistically significant among diseased and control groups He pointed out that values for the two groups are scattered over the same range and have little diagnostic or prognostic significance for any given individual I would like to reemphasize that, strictly speaking surveys of characteristics are not epidemiological studies they do not relate the disease to specific environmental or genetic factors which characterize the populations under investigation He pointed out that in many studies biochemical determinations have been substituted either for an adequate study of the factors or for an *ultimate* appraisal of the clinical manifestations of the disease

In the area of epidemiology and particularly in heart disease *there* are several things that need to be said *about* the viewpoint of those who work *in* epidemiology and who have epidemiological studies going on in are

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On the third day of the Conference

uch as heart di ea e cancer auto mobile accident cerebral pal y and birth defects All the e tudies have a common denominator I think it is particularly important that we talk about the methods of epidemiology because intrin ic in the e tudies is the u e of statistical method

Unfortunately certain groups in our country feel strongly that tati tical tudies on man are of relatively little value and inconclu ive These groups believe that the true facts can be a cer tained only by animal experimentation and clinical ob ervation This is not aid in criticism this is merely an ob ervation We are often urged to take no public health action until lab oratory and clinical tudies have given ultimate an wers about the nature of uch di ea e as cancer This attack on the public health approach expres es a belief that is widely held I think perhaps for that rea on it is important to point out that epidemiological studies on man have been highly productive of scientific knowledge and of practical applic ation in the advance of medical cience This does not in any way dep recate the value of animal experimen tation in the laboratory or clinical in ve tigation in the ward I think these things are indi pen able and certainly nece ary for medical progre s But we mu t empha ize the true value of the epidemiological approach with its heavy reliance on tati tical compilation in the analy is of events that occur in human population

I would like to make another point here that has not been mentioned in the la t two days of discu sion and that is the interchangeability of medical tati ticians and epidemiologists The medical stati tician is u ually called a bio tati tician and is first of all a mathematician who adapts his knowl edge to the tudy of di ea e The epi demiologi t on the other hand is killed in medicine but ha learned to adopt a mathematical approach in the tudy of disea e among groups of people Certainly whenever pos ible the two work together in the proces the tati tician becomes a better epidemiologi t and the epidemiologi t a better stati ti cian so that the two ultimately approach one another clo ely in their skills Since the di tinguishing feature of an epi demiological study is its u e of numbers and their analysis by stati tical method and logic it seem permi sible in the present di cu sion and in our future di cu sions in this area to u e the word bio tatistics and epidemiology almo t interchangeably

Without going into great detail I think it would be wise for all of u intere ted in epidemiology to go back to the era preceding knowledge of the bacterial and viral cau es of di ease to ee the way in which some of the early workers u ed epidemiological methods When Jenner did his work on mallpox 161 year ago he handled his accounts and compiled his cases in uch a way that he really carried out a neat epi demiological study He knew nothing about the cau e of the di ea e and yet he found out how to prevent the di ea e John Snow s cla ic tudies on cholera in 1854 are a parallel with what we are facing today in heart di ease Many of the same puzzles were faced by John Snow in hi attempt to work out the relationships betwe n chole ra and the way in which the disease was trans mitted Michael Taylor in England tudied epidemics of typhoid fever in 1857 and traced its transmission through milk Again he knew little about the cau e but he knew how to develop meaningful a ociations So as we trace epidemics back through the last century we find many individual inve tigators confronted with precisely the same types of problems that we are facing at the present time in heart di ease

To bring this viewpoint up to date I hould like to point out that our

knowledge of carcinogenic agents and the mean of preventing certain types of *neoplastic di ease to the extent that* we can is largely the product of epi demiological studies Certainly the early studies on scrotal cancer in chimney sweeps on cancer from contact with pindle oil on cancer of the bladder of aniline workers and on kin cancer from arsenic are all examples of the epidemiological approach Many of you are familiar with some of the recent reports on the development of leukemia among tho e treated with x rays for spondyliti the effects on children of irradiation of the thymu and the in crease of congenital deformities among babies who e mothers had pelvic x ray examination during pregnancy Again the e are examples of the method we are talking about

I would like to read a hort quotation from Dr Frost one of our foremo t epidemiologi t who was my profes or of epidemiology at the Johns Hopkin School of Hygiene and Public Health He aid The opinion is more or le s *prevalent that inference based upon epi* demiological argument cannot Fe truly conclu ive becau e the evidence is purely circum tantial Such opinion has frequently failed to take account of the whole ma s of evidence and to follow the argument which is neces arily built up step by tep in its somewhat com plex and perhaps tedious way Given sufficient cope and accuracy of observa tion a conclusion as to the nature and pread of di ea e may often be estab li he l quite firmly by circum tantial evidence well in advance of experi mental confirmation Moreover many problem of disea e tran mis ion which are highly important from the tand point of prevention are of a type that can Fe solved only by investigation of this kind The weakness in conclu ions drawn from circum tantial tudies is u ually chargeable not to l a ic defect in the method of investigation l ut more often to paucity or inaccuracy of data or to fal e logic in their inter *pretation*

Finally I would like to say that in talking about epidemiology we mu t be cautious about the use of the word We hear about shoeleather epidemi ologi ts who go out into the field and learn things by doing their own work We hear about armchair epidemi ologi t who have others gather their data Now we have heard recently about clinical epidemiology Dr John Paul of Yale has ju t publi hed a book* with that title We hear al o of experi mental epidemiology The point I wi h to make here is that we need to con ider epidemiology in it total context

We al o need to realize that many heart di ea e tudies labeled epidemi ological do not actually follow epi demiological methods in their design or execution There is no reason why every study which ets out to de cribe characteri tics of person with heart di ea e hould Fe called an epidemi ological tudy It i my hope that when *clinical and laboratory* researchers de sign an f carry out epidemiological studies they take care to tudy carefully and follow epidemiological method Only when a tudy employ epidemi ological m thod hould it Fe labeled epidemiological

Good epidemiological tudies are very difficult in coronary heart di ea e be cau e the preclinical stages of athero clero i —the precursor of coronary heart disea e—appear to be occurring almo t univer ally among our adult pop ulation in the United State When a disea e is almost univer al the com pari on of ca es and noncases Fecome almo t impos ible except in po t mortem tudies Yet the compari on of ca e with nonca e comprises the l a ic method of epidemiology

Difficulties notwith tandin there re

* Paul John R Cl al Epi l m logy U ve s ty of Ch ago P ess 19-8